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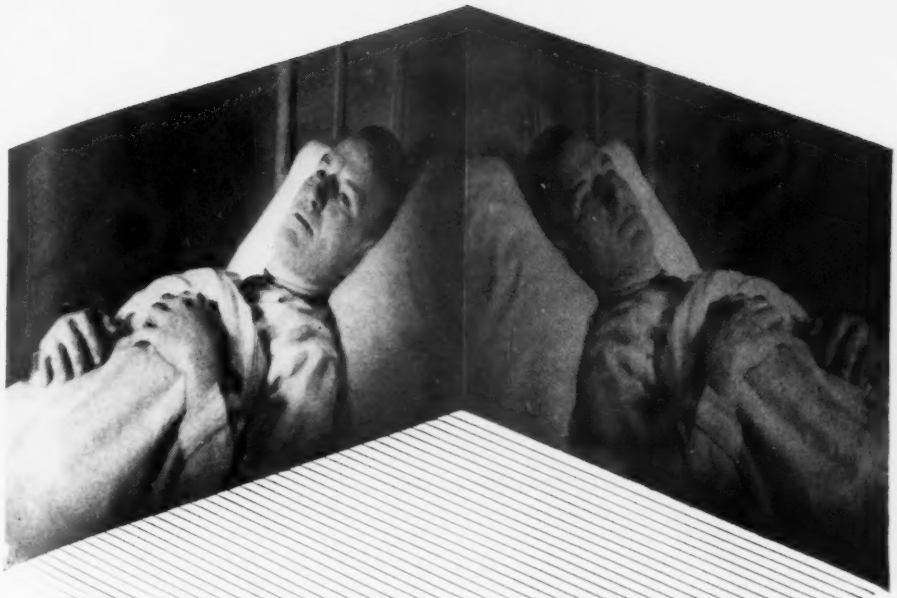

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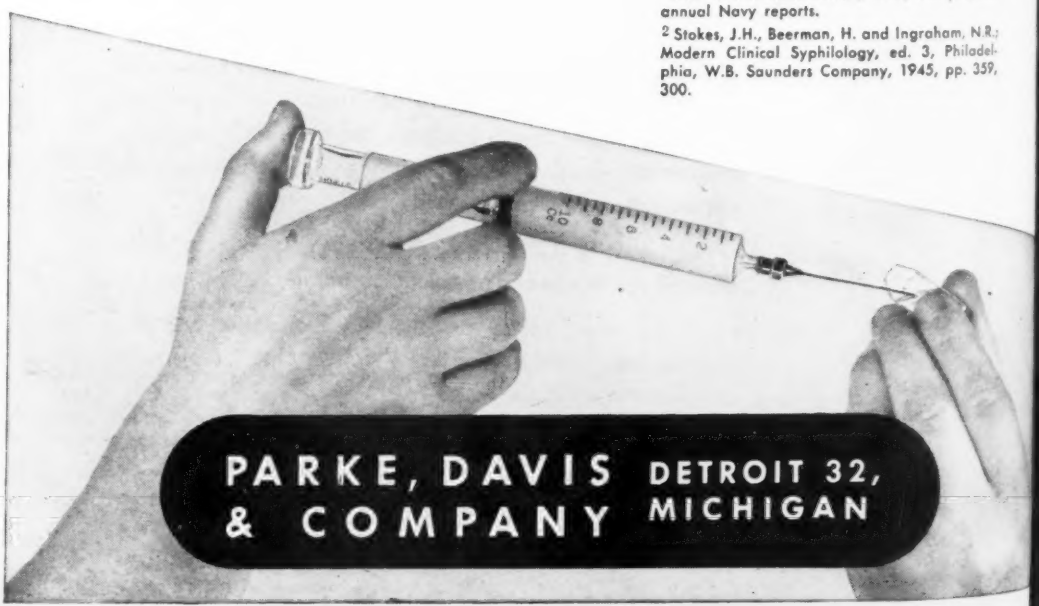
[1] U.S. Nav. M. Bull. 45:783, 1945, and previous annual Navy reports.

[2] Stokes, J.H., Beerman, H. and Ingraham, N.R.: Modern Clinical Syphilology, ed. 3, Philadelphia, W.B. Saunders Company, 1945, pp. 359, 300.



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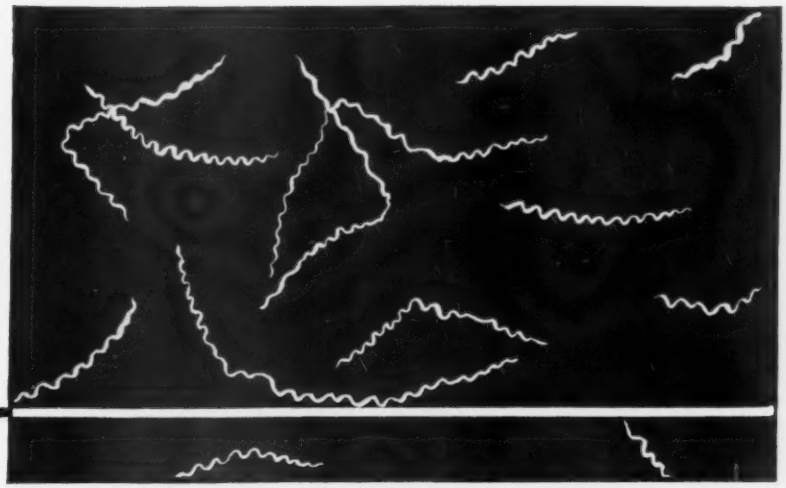

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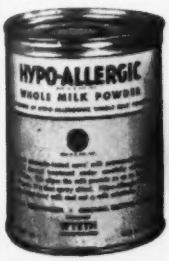

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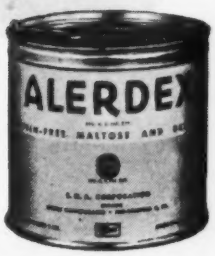

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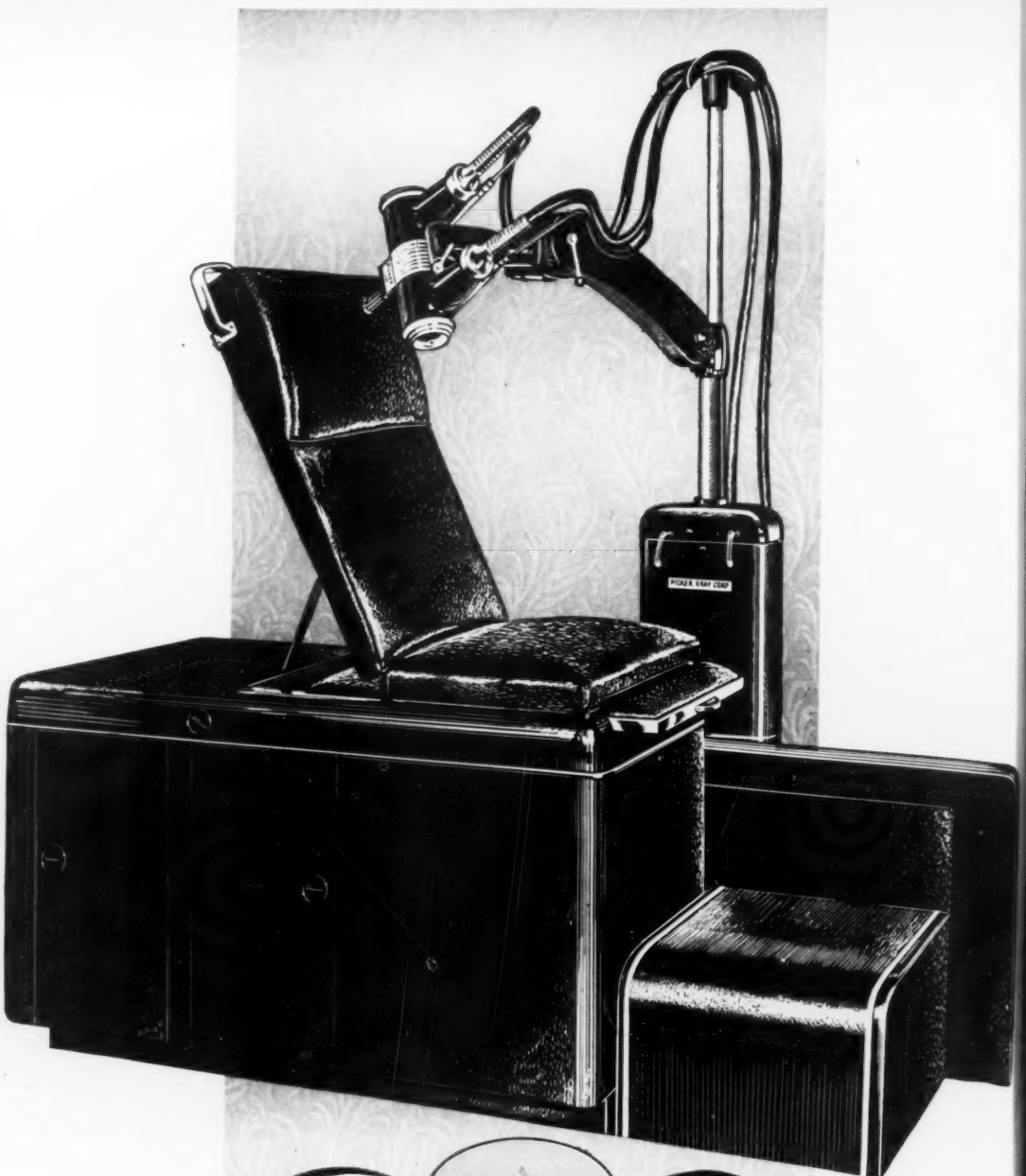

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Archives of Dermatology and Syphilology

VOLUME 53 JUNE 1946 NUMBER 6

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SYMPOSIUM ON DIAGNOSIS AND TREATMENT OF CUTANEOUS CANCER

CUTANEOUS CANCER FROM THE STANDPOINT OF THE DERMATOLOGIST

EUGENE F. TRAUB, M.D.
NEW YORK

THE subject cutaneous cancer is to be discussed from various points of view, particularly with regard to modes of treatment. In the limited time at my disposal, I felt it was probably best to discuss only the various types of basal cell and squamous cell cancer.

Basal cell epithelioma is found most frequently on the face, 95 per cent of the lesions occurring above the angle of the mouth, particularly about the nose and eyes. With rare exceptions, this type of cancer does not metastasize; hence it may, on the whole, be looked on as a local disease in the majority of cases. It grows slowly, some lesions taking years to attain a diameter of 1 or 2 cm. Many types of basal cell epithelioma respond to treatment more readily than do ordinary warts. Because of these facts, namely the location of the cancer on the face, the relative ease of treatment and in most instances the lack of danger of the process itself, basal cell epithelioma must be looked on as a disease of mild grade malignancy and its local destruction should be carried out with two major ideas in mind: first, a complete destruction of the lesion itself and, second, and almost as important, destruction of the lesion with a minimum of damage to the surrounding tissues, so that an excellent cosmetic result occurs. Another consideration is that the method of treatment adopted should be such that no future danger to that area of skin will arise as a result of the treatment. It therefore becomes imperative for one to weigh and select each case carefully, taking into consideration the age of the patient, the location of the lesion and its proximity to bone, cartilage, eyeballs and other parts of the body.

This paper is the first in a "Symposium on Diagnosis and Treatment of Cutaneous Cancer," held at the New York Academy of Medicine, Section of Dermatology and Syphilis, on April 4, 1944.

Basal cell epitheliomas occur in many different patterns or types, and these vary materially in response to the different types of therapy. For example, for convenience, both in diagnosis and in treatment, I have classified the basal cell epitheliomas into the following types:

1. Rodent ulcer, or hard pearly bordered lesion
2. Morphea-like type
3. Soft nodular type
4. Pigmented type
5. Superficial cicatrizing type
6. Cystic type
7. Infiltrating or invasive type
8. Multiple basal cell epithelioma

Every one is familiar with the various lesions of the rodent ulcer type, of which some are relatively soft and others have a hard, rolled, almost cartilaginous-like border. The central ulceration not infrequently may be covered with a crust, which should always be removed both to assist in the diagnosis and to facilitate treatment. This variety of basal cell lesion usually responds well to radiation of all types—by that I mean various types of roentgen rays either filtered or unfiltered, low voltage or contact, etc., and radium. It should be a cardinal rule, however, that with whatever type of treatment is selected for a given lesion the lesion should be destroyed in one treatment. While I appreciate the fact that this quick destruction cannot invariably be accomplished, I make it my aim to destroy at least 95 per cent of all basal cell lesions at the time of the first treatment. This means that one must carefully weigh the type of treatment to be used. If roentgen rays are selected and the dose to be used for a given patient to achieve a cure in one treatment seems to be excessive and liable to give rise to so much damage of the skin that the later development of a squamous cell epithelioma may be expected, then that method of treatment is, in my opinion, not suitable. On the other hand, the lesion may not be ideally located for surgical excision. Furthermore, surgical excision and repair may necessitate repeated operation with hospitalization. This should not generally be necessary in the treatment of the usual basal cell lesion.

The dermatologist has, for many years, combined the several types of destruction of such lesions because the cosmetic results achieved in this way are far superior to those achieved by only one method of attack. For example, if the rodent ulcer has an unusually hard and deep rolled pearly border and base, it is a simple matter for one to anesthetize the lesion with procaine hydrochloride and desiccate the hard portion of the lesion. A curet is then employed to remove the desiccated tissue, and by experience one can easily determine when all the cancer tissue has been removed. The lesion is then ready for a dose of roentgen rays or radium, but with this combined method a large dose is not necessary and as a result no sequelae of unpleasant radiation need be

expected. An excellent cosmetic result is achieved, and the patient is cured with little or no deformity. This procedure is particularly suitable for basal cell lesions located on or about the eyelids or the corners of the eyes and on or about the ears at points where cartilage may be destroyed by large doses of radiation, and the same situation of course will apply to lesions of the nose.

The morphea-like basal cell lesion is one that is not usually radiosensitive, and for this reason I believe that lesions of this type are best treated by either surgical excision or excision with the electric knife. As these lesions are flat hard areas with little elevation but with considerable depth and a shiny glazed surface, the patient may permit them to reach considerable size before consulting his physician. As a result, if the lesion is surgically excised, considerable plastic repair generally must be done, and if a surgeon tries to remove as little tissue as possible, fearing that closure will be difficult, a recurrence of the lesion may be expected. For this reason, I have frequently found it advisable to remove these lesions with the electric cutting current, allowing the area to fill in with granulation tissue; and if the resultant scar is not satisfactory it may be removed at a later date for cosmetic purposes. Meanwhile, the patient can be kept under observation to be sure that the cancer has been completely destroyed. While this method might require a second operation if the cosmetic result were not satisfactory, the situation would be no different than if the growth were removed surgically and several plastic repairs made.

The soft nodular type of lesion is radiosensitive and can almost invariably be destroyed in one treatment with a moderate dose of the roentgen rays or radium. The pigmented variety also is usually radiosensitive, or if not it can easily be destroyed by the combined treatment described for the rodent ulcer type.

The superficial cicatrizing type of lesion is seen most commonly on the trunk or the extremities. While this type is said to be radioresistant, it has responded to relatively small doses of radiation in my experience and certainly can easily be destroyed by a combination of desiccation, curettement and radiation.

Lesions of the cystic type are frequently deep seated and when occurring about the eyelids may be hard to destroy by radiation alone. Here again a combination treatment is ideal.

The infiltrating or invasive type of growth, especially if extensive, can frequently be cured by radiation, but if one does not succeed in doing this after giving one or two doses of radiation then I believe that the lesion should be completely excised by the electric cutting current or by surgical intervention.

Multiple basal cell epitheliomas occur mainly on the trunk, but they may appear also on the face. They do not represent a special type

but are a variety of one or more of the types previously mentioned and must be treated accordingly.

While it has always been the argument of the surgeon that cancer should be removed radically by some cleancut method, such criticism can no longer be leveled at the present day technic of adequate desiccation and curettement, followed by a destructive radiation. As stated earlier, this method is superior to any other in properly selected cases. It avoids the disadvantages of surgical treatment with the knife and the overirradiation that is frequently necessary to cure a lesion in a single sitting, and it gives a cosmetic result so good that it is frequently difficult to locate the treated area. The dermatologist who has specialized in this method and whose technic has been perfected by a combination of surgical and radiotherapeutic training is the ideal one to carry out the method.

I shall now discuss briefly squamous cell epitheliomas of the skin. These lesions differ from the basal cell growths in two major respects. First, they develop rapidly. Second, and most important, the removal of the primary lesion represents only a portion of the possible job to be undertaken. For this reason it is my opinion that most dermatologists, unless fitted by special training in work with cancer, generally are not qualified to treat these growths. Most dermatologists, however, restrict themselves to the treatment of basal cell lesions and of those squamous cell lesions and epitheliomas in which it may be reasonably assumed that the disease has not progressed beyond the primary lesion. There is another type of case in which the dermatologist might be called on to treat a cutaneous cancer but because the growth is considered inoperable he, therefore, must use the radiation at his disposal to palliate rather than to cure the disease.

While the majority of the cancers on the face, especially those above the angle of the mouth, are of the basal cell type, at least 95 per cent of those occurring on the extremities are squamous cell ones. I believe it is probable that squamous cell lesions on the face above the angle of the mouth occur in slightly more than 5 per cent of cases and that one does not see basal cell lesions occurring on the extremities in as high as 5 per cent. Squamous cell lesions, therefore, are encountered most frequently on the extremities on the mucous membrane surfaces and as a sequel to other dermatoses. The lesions of the mucous membranes whether located on the lip, buccal mucosa, tongue or genitalia, should not, in my opinion, be handled by the dermatologist. My reason for this statement is that metastasis from such primary sites may occur as early as three or four weeks after the lesion has been discovered by the patient and that what may seem to be an early lesion is actually a late one. There is no doubt that the primary lesion can be destroyed by

the dermatologist as well as by the surgeon or the radiotherapeutist, but if the lymph nodes are to be treated by dissection he is generally unqualified.

The early squamous cell lesion of the glabrous skin, occurring particularly on some portion of the face, is a lesion that I believe dermatologists are qualified to treat. This is the lesion which is frequently not recognized and yet presents just as typical a clinical appearance as do most of the types of basal cell lesions.

DESCRIPTION OF THE TYPICAL LESION

The development of the nodule is usually rapid, beginning frequently as a papular lesion of pinhead size and reaching a diameter of 1 to 2 cm. in from three to six weeks. After this period, the growth is somewhat slower. In patients under 45 to 50 years of age it is more rapid than in older ones. The typical squamous cell epithelioma of the glabrous skin begins first as a small grayish nodule covered with a scale or crust. As it increases in extent and depth, the crest assumes a reddish color and may become ulcerated or verrucous. The tumor which develops is hard, firmly embedded in the skin and yet protuberant. Its raised, bulging border presents a glazed or waxy appearance. The presence of numerous small blood vessels in the border gives the base an acute inflammatory appearance which is characteristic. The upper and outer portion of the border is usually more or less hyperkeratotic, and in the central area an erosion appears. The latter develops into a crater-shaped ulceration which is irregular, fissured and grayish and bleeds easily even on slight irritation. The appearance of the lesion at this stage may easily simulate that of a large infected verruca, sebaceous cyst or a tumor of large molluscum contagiosum. The vascularity of the base of the growth gives the appearance of an infection. On the floor of the central crater there can be seen yellowish gray granules or material simulating the cheesy contents of an infected sebaceous cyst. The latter substance is composed of horny cells and epidermic globules.

Little mention is made of this growth in most of the dermatologic or surgical textbooks. When the lesion has been described, the author has frequently expressed the opinion that metastasis may occur early to the regional lymph nodes. This was Darier's [1] belief, but he also expressed the opinion that generalization to the viscera was rare. In all the patients which I have seen, I have encountered only 1 instance of local metastasis to a regional lymph node, and when this node was excised the patient remained free of further cancer for a

1. Darier, J.: Text-Book of Dermatology, translated from the French by S. Pollitzer, ed. 2, Philadelphia, Lea & Febiger, 1920.

period of three years, during which I was able to follow him. My interest in this type of lesion dates back over twelve years, and in 1933 Dr. Tolmach and I [2] reported on 26 cases of similar lesions and our method of removal.

Briefly, the method of treatment that we suggested consisted of excision with the electric cutting current. At first we felt that it might be advisable to follow such excision with radiation, but, as most of the lesions can be easily excised in toto, there seemed to be no point in following a complete excision by irradiation. Therefore, only when one is uncertain whether the excision is complete need the excision be followed by irradiation. In most of our cases, in all of which the development was early—not over three months—it was not found necessary to either irradiate or excise the nodes.

Little need be said about squamous cell lesions involving cartilage, because I believe that they require surgical excision.

In dealing with lesions on the extremities, particularly on the dorsal surface of the hands, the local lesion may be excised in toto by the dermatologist if the lesion is early and if no metastasis in a node can be palpated. On receipt of the report of the pathologist, should the lesion be of the more malignant type, consultation with the surgeon as to further disposition of the case may be advisable. If the lesion on the extremity is of long standing and if there is no doubt that metastasis has occurred, then certainly the entire management should be turned over to the surgeon.

Squamous cell cancer occurring as a sequel to other dermatoses should be managed much as I have suggested for lesions on the extremities. When the change to cancer is suspected, the lesion is small and metastasis not apparent and the diagnosis still needs microscopic confirmation, it is frequently better for the dermatologist to excise the entire lesion than to perform a diagnostic biopsy. The reason that I prefer this procedure to performing an ordinary punch biopsy is that so frequently with a punch biopsy or excision of a small portion of tissue one does not obtain sufficient material for a conclusive diagnosis or the tissue may be taken from a portion of the lesion not characteristic of the entire mass; hence it might become necessary to perform several biopsies, with the loss of valuable time, before a correct conception of the growth may be obtained. All such difficulties are obviated by excising the entire lesion and examining it in toto.

2. Traub, E. F., and Tolmach, J. A.: Squamous Cell Epitheliomata of the Skin of the Face, New York State J. Med. **33**:875 (July 15) 1933.

SUMMARY

1. The dermatologist is, in my opinion, best qualified from the standpoint of his diagnostic and therapeutic training to treat basal cell cancer. He is not limited to surgical methods as the surgeon is nor is he limited to radiation therapy only, as is the radiotherapeutist. He is able to remove and at the same time irradiate basal cell cancer, achieving through office treatment what the surgeon frequently can do only after repeated operations and hospitalization and what the radiotherapeutist can do only after a loss of time and a dosage that may well pass the limit of advisability.

2. He is able to destroy basal cell lesions at one sitting with a cosmetic result that cannot be surpassed.

3. The dermatologist is qualified to treat early squamous cell epithelioma of the glabrous skin. He is able to make a diagnosis early and to treat an early squamous cell epithelioma which is superimposed on precancerous dermatoses.

EARLY DIAGNOSIS OF CANCER OF THE SKIN

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AT THE beginning, cancer of the skin proper must be distinguished from cancer of the mucocutaneous junctions. The dermatologist is often called on to diagnose cancer of the lips, tongue, floor of the mouth and buccal mucosa, cancer of the mammary gland and cancer of the genitals and rectum. He must be familiar with these cancers, and in their diagnosis his opinion is often given much weight; but the time tonight will be devoted to a discussion of cancer of the skin proper, and I will speak for only a few moments on its recognition and diagnosis. It is commonly known that skin of certain types is predisposed to the growth of cancer. There is probably no fact regarding the cause of cancer better established than that habitual exposure to sunlight of a fair sensitive skin and maturity are factors that together favor the development of cutaneous cancer. One third of all cancers of the skin occur on the nose and cancer is common on the rim of the ear. In a category similar to that of farmers' and sailors' skin is the cancer which occurs in xeroderma pigmentosum and in chronic radiodermatitis. Moreover, the likelihood of cancer is augmented if, in addition, there are moles, warts or other so-called precancerous lesions present and also if there is contact, occupationally or otherwise, with arsenic or with pitch, tar, paraffin, lubricating oils or other hydrocarbons containing dibenzanthracene or similar carcinogenic substances.

The early symptoms of basal cell epithelioma should now be considered because this disease is so common. Basal cell epithelioma develops on an inconspicuous slightly erythematous scaly spot, which becomes a little thickened, glistening and waxy. The thickening may be so slight that it is barely perceptible. The waxy color is of glistening semitranslucence or of a pearly appearance. The earliest lesions are like small inverted buttons, slightly elevated above the surface of the skin. Small waxy papules coalesce to form a plaquelike lesion, and at the border of this similar papules fuse and produce an elevated rolled border. The central portion becomes crusted, and when this crust is knocked off or pulled off there is bleeding; another crust forms, and

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this sequence of events continues. In crusted lesions, the waxy color may not be apparent until the crust has been removed. The duration is usually a matter of years, sometimes of only a few months and often of many years.

In addition to the common button type and plaque type basal cell epitheliomas, there are many other clinical types, of which the rodent ulcer is the most important. It is a burrowing, mutilating, destructive growth which occurs mostly about the eyes, the ears or the nose. In these locations, it may cause complete destruction of the orbital contents or of the external ear or nose. It may even cause death through intercurrent disease, such as erysipelas, bronchial pneumonia, sinus thrombosis, epidural abscess or meningitis. The ulceration is deep and punched-out like a gumma. The floor of the ulcer is dirty, and the edges are crusted. After the crust has been removed, a rolled waxy border may be discernible. The long duration and the presence of this waxy border may warrant the clinical diagnosis of rodent ulcer, but this must be confirmed by biopsy.

Many other clinical varieties of basal cell epitheliomas are definite entities, but there is not sufficient time to go into the details of all of these. Cancers of the cicatrizing, or scar-forming type all possess the essential characteristics—waxy, glistening appearance, rolled border and a tendency to form crusts and to bleed occasionally. Microscopic study of these lesions reveals many differences between the individual growths, and one feature which is important is the presence in many of these lesions of squamous cell proliferation. Such growths are classified as mixed basosquamous cell epitheliomas. Their importance lies in their clinical resemblance to pure basal cell epitheliomas and their occasional recalcitrance to treatment. Rarely if ever do basal cell epitheliomas metastasize, but sometimes the squamous cell portions of mixed basosquamous growths follow a clinical course like that of squamous cell epithelioma.

The distribution of basal cell epitheliomas is chiefly over the upper portion of the face, above the line drawn from the corner of the mouth to the lobe of the ear, being specially common on the nose, lower eyelid, forehead, cheeks and ears. However, they can occur, and often do, on the chin and less frequently on other parts of the integument. The adenoid type is found chiefly on the forehead or scalp or near the eyes.

Squamous cell epithelioma is sometimes like the waxy growth of basal cell epithelioma, but more often, and more characteristically the squamous cell epithelioma is a warty growth. One must keep in mind the fact that I am speaking of squamous cell epithelioma of the skin

proper and not of squamous cell epithelioma of the mucocutaneous surfaces.

On the skin proper, where the lesion is dry, there is much cornification. The horny part of the growth, which gives the wartlike appearance, is due to dyskeratosis, and this horny projection is an inherent part of the tumor. It is thus entirely different from the loosely attached crust of the basal cell epithelioma. Although this horny projection resembles a wart, it differs from a wart in that it arises from an indurated tumor base. If the squamous cell epithelioma is diagnosed in this early, warty stage, the prognosis for treatment is excellent. In the course of time, if the lesion is not treated at this early stage the horny projection is knocked or picked off, with resulting ulceration and eventually induration develops in the underlying tissues and metastasis may occur. The mortality from epithelioma of the skin, however, is low, being under 2 per cent; cancers on the fingers and hands are the most likely to metastasize.

CUTANEOUS CANCER FROM THE SURGEON'S POINT OF VIEW

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IN the treatment of carcinoma of the skin I feel that cauterization of the lesions alone is not the treatment of choice. Unless it is thoroughly done, the treatment is inaccurate and often ineffectual, and if carried to a depth sufficient to destroy the disease unsightly scarring results. Healing is delayed; the period of dressings may be long, and there is no certainty that the disease has been completely eliminated as there can be no study of sections of the tissue destroyed.

The two main methods of treatment of carcinoma of the skin are irradiation and surgical excision.

In the earlier smaller lesions there are certain locations where irradiation is preferable to surgical treatment because of the difficulty of excising the lesion adequately without causing deformity or without complicated plastic procedures. A sample of such a location is the tip of the nose. There are other locations, such as the external auricle, where irradiation may cause a chondritis that becomes painful and difficult to heal.

Many radiosensitive epitheliomas are eliminated by irradiation without noticeable scarring; those that are radioresistant may be difficult to eliminate by this means. With surgical treatment—inasmuch as the majority of epitheliomas occur in the later decades of life, the subcutaneous fat is atrophied and the skin is loose—excision in the form of an ellipse with extensive undermining of the skin allows closure to be made more readily in this class of patients and with less resultant scarring than in those in the earlier decades of life. Irradiation sufficient to eliminate the disease may injure underlying tissue and may cause later sclerosis of the skin, pigmentation, telangiectasia, ulceration or even epithelioma. No such complications occur after surgical intervention, and the treatment of these complications should be surgical. Keloids occur but rarely and fine inconspicuous scars usually result from surgical treatment.

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Within recent years improvements in technic in the treatment of these lesions by irradiation have made it possible to eliminate the disease more certainly and with less deformity than in the past. On the other hand, a greater knowledge of plastic procedures for closure is more widespread among surgeons, and less decided deformities result from surgical methods nowadays than formerly.

Information regarding the nature of the lesion cannot be obtained if irradiation alone is used to eradicate the disease. Even if a biopsy previous to irradiation is made, such a biopsy may not always show the complete picture of the malignant process. Possibly the scarring from irradiation may be a more conspicuous deformity than that produced by surgical excision with plastic closure. In small lesions biopsy excision—that is, elimination of the lesion by a sufficiently wide margin to excise it completely—has the advantage of making possible the microscopic study of the lesion, the determination by the pathologist that the lesion was completely excised, and the character of the lesion so that one is able to determine whether metastases may be expected. This is also true of the larger lesions. It is possible, therefore, for the pathologist to advise the surgeon that dissection of regional nodes should be performed. There is an uncertainty about the elimination of the disease by irradiation that is absent with wide excision and careful study of the specimen. The patient's mind can be put at rest with a favorable report from the pathologist.

In each case the first aim of the dermatologist, the radiotherapeutist and the surgeon should be complete eradication of the lesion at the first treatment. Ineffectual irradiation may cause the cells to become more resistant to subsequent irradiation, and I feel strongly that if the first irradiation is not successful it is better to resort to surgical intervention at once rather than to continue ineffectual irradiation. The greater the amount of irradiation, the more difficult becomes the plastic problem of obtaining healing with primary closure, with free grafts and with pedicle flaps to fill the defect after excision. On the other hand, excision should be sufficiently wide to eliminate the disease at the first attack. In certain instances, if the pathologist finds that the tumor has been cut into and indicates the location on the piece excised, further excision may be made and the disease may be eliminated. This, however, should be infrequent if the surgeon is imbued first with the necessity of taking a wide enough margin of normal tissue to make sure that the excision is well beyond the tumor. His second objective should be that of restoring the part to its normal condition insofar as it is humanly possible. The surgeon who has the various principles and procedures of plastic repair in his armamentarium is a safer operator than the surgeon who lacks this knowledge, as the former can afford to take

wide enough areas to eliminate the disease, because he knows that he can restore the part by one of several methods with comparatively little deformity in most cases. The surgeon without this knowledge tends to cut too close to the tumor for fear that he will not be able to close it without great deformity, and, frequently, insufficient tissue is excised, with resultant recurrence.

The pathologist, the dermatologist or radiotherapeutist and the surgeon should know what can be done by each method of treatment; they should meet in the clinic and consult with an impartial point of view to determine which procedure, irradiation or surgical treatment, is indicated from the standpoint of the patient's best interests. In private practice the questionable case should be referred for opinion. It would also be of value to the surgeon and radiotherapeutist to see cases with the dermatologist in order to become familiar with lesions which simulate epitheliomas. It is doubtless true that an expert radiotherapeutist is better than a poor surgeon and a capable surgeon is better than a poor radiotherapeutist.

TREATMENT OF CUTANEOUS EPITHELIOMA

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EPITHELIOMA of the skin may be successfully treated by various means, and no hard and fast rules should be established. The surgeon who is familiar with the advantages and disadvantages of each method has a greater chance of attaining good results than the surgeon whose experience is limited. Obviously this requires a knowledge of the peculiarities of behavior of the various types of cancer and the limitations which the location of the cancer imposes on the treatment chosen.

ROENTGEN RAY THERAPY OF EPITHELIOMAS OF THE SKIN

High Voltage Roentgen Rays.—Roentgen rays with a peak kilovoltage of 200 kilovolts or more are seldom used in the treatment of cutaneous cancer, except for deeply infiltrating epitheliomas. It is impossible to sterilize metastatic epidermoid carcinoma in lymph nodes by high voltage roentgen irradiation therapy alone. While this treatment does exercise a restraint on growth to some extent, it should be recognized as a palliative treatment only. For curative attempts high voltage roentgen ray therapy should be supplemented by interstitial irradiation or radical surgical dissection.

Low Voltage Roentgen Rays.—Roentgen rays with a peak kilovoltage of 100 to 140 kilovolts are of great value in the treatment of cutaneous cancer. A target-skin distance of 30 to 40 cm. is used, either without a filter or with 1 to 2 mm. of aluminum added, depending on the depth dose desired. Thick or deeply infiltrating cancers require an increased depth dose, which is obtained by the use of higher voltage, greater target-skin distance and heavier filters. Superficial cancers need lower voltage, shorter target-skin distance and less filter or no filter at all.

The normal skin surrounding an epithelioma is shielded with lead during roentgen ray treatment. If roentgen rays of low intensity (100 kilovolts) are used, 1 mm. of lead will remove more than 99 per cent

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From the Mixed Tumor Service of the Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York.

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of the radiation, although half this thickness is usually employed. This sheet lead foil, 0.5 cm. in thickness, is easily cut and molded to fit each individual epithelioma, leaving an additional 5 mm. or more in width on all sides of the margin of the lesion. The lead protective shield is held in place with adhesive plaster or by contact pressure from various-sized cylinders, which are attached to the open port for the purpose of limiting the field of irradiation. Correction in the roentgen dose at the surface must be made when these shields and cones are used, because only the central portion of the beam is utilized. It is a well known physical law that the smaller the field the less the depth dose obtained, owing largely to a decrease in the scattered tissue radiation.

Low voltage roentgen irradiation requires a greater number of roentgen units to cure an epithelioma of the skin than higher voltage roentgen irradiation. The epitheliomas may be treated by daily fractional doses of 250 to 350 until the total dose approximates 2,500 to 4,000. When epitheliomas of the face are treated, the total dose may be increased by at least 50 per cent. Cancers of the face can readily be treated at a single sitting if no filtration is used.

MacComb has determined the erythema dose for different-sized skin portals when the roentgen rays are generated at 100 kilovolts and 5 milliamperes, giving an intensity of 270 r per minute at 30 cm. target-skin distance without filter. The half-value layer of the radiation was 1 mm. of aluminum. He found that for skin portals with diameters of 0.5 cm., 1 cm. and 2 cm. 350 r produced an erythema in 80 per cent of the cases. For fields or portals of 3 and 4.5 cm. in diameter, 280 r gave an erythema. This principle was applied to the treatment of a series of 50 patients with epitheliomas of the skin. Not one of the epitheliomas exhibited satisfactory regression when the dose was less than 12½ threshold erythema doses. On the basis of these results, MacComb constructed a table in which the given doses were considered sufficient for epitheliomas of various diameters.

Chaoul Contact or Short-Distance Roentgen Therapy.—The Chaoul x-ray outfit is limited to a voltage range of 50 to 60 kilovolts. The thin copper filter (0.2 mm.) or transmission anode is so placed that the tube operates at contact or 3 to 5 cm. target-skin distance. It has applicators of various sizes and shapes to be placed against the epitheliomas. A soft beam is utilized, and these rays are largely absorbed in the superficial tissues, i. e., the cancer. For contact application, the rate of emission is approximately 800 r per minute; for a target-skin distance of 3 cm., it is 88 r per minute, and for a target-skin distance of 5 cm., it is 36 r per minute. Daily fractions of 250 to 400 r units are given, with total doses ranging anywhere from 3,000 r units. Epitheliomas on the face may receive the total dose at a single exposure; for contact application this is seldom more than 3,000 r.

This apparatus has a special usefulness only for the treatment of superficial cancers. Because the depth dose is not great and the major portion of the radiant energy is absorbed by the tumor proper, the deep structures are uninjured and the hazards of late radiation necrosis are considerably lessened. The reaction is sharply localized around the cancer.

Philips Contact Roentgen Ray Therapy.—The indications are the same as those for the Chaoul machine. The inherent filter of the tube and shock-proof shield is the equivalent of only 0.2 mm. of aluminum. If additional filtration is necessary, disks of aluminum of 1 or 2.5 mm. thick may be inserted over the end of the tube and held in place by attached treatment cones. The diameter of the emergent roentgen ray beam is slightly less than 2 inches (5 cm.). The intensity is always at 50 kilovolts constant potential. Two milliamperes is the current employed, although the tube is capable of functioning at 3 milliamperes if the time of treatment is short. The distance of the focus from the target to the protection cap over the end of the tube is 18 mm. Over this end is placed a localizing cone, which increases the target-skin distance to 2 cm. The actual tube is within a long light metal cylinder, which is handled at will by means of an attached grip. The dose administered to epitheliomas of the skin ranges from 3,000 to 8,000 r units, usually in fractions of 400 r units.

Radium.—At the Memorial Hospital for the Treatment of Cancer and Allied Diseases there are four standard radium applicators in general use, and their different surface areas render them suitable for treating many small cutaneous cancers.

The filtration of these plaques is equivalent to 3 mm. of brass, which is the total filtration of the radium or radon capsule—usually 0.2 to 0.5 mm. of platinum—plus the thickness of the brass case of the plaque. The plaques are applied at a distance of 1 cm, with the exception of the tray, which has a radium-skin distance of 3 cm. Small blocks of balsa wood or Bakelite are used to maintain this distance. The region surrounding the cancer is shielded by heavy lead to protect the normal adjacent tissues.

A cutaneous cancer which is more than 1 cm. in thickness or shows deeply infiltrating properties should not be treated with radium at contact or at a radium-skin distance of 1 cm., as it delivers only 30 per cent of the skin dose when the radium plaque is used. The dose at a depth of 1 cm. when the radium tray is employed at a 3 cm. radium-skin distance is 62 per cent and therefore offers a better method of treatment for the deeper epitheliomas. All epitheliomas which are more than 1 cm. in thickness or measure more than 3 cm. in diameter should be treated by low voltage (100 kilovolts) roentgen rays.

Radium Moulage.—Whenever contact application of radium is desired over very irregular surfaces, the moulage of a dental modeling compound or wax is a valuable adjunct to radiation therapy. The radium tubes of 0.2 to 0.5 mm. of platinum filtration are held in direct contact with the uneven contour of the epithelioma. The dose is computed on the basis of 75 to 100 millicurie hours per square centimeter, with the smaller dose used when the cancer covers a larger area. A dose of 15 millicurie hours per square centimeter applied by contact with a 0.5 mm. platinum-filtered radon tube is equal to 1 threshold erythema dose. Penetration of the radiating beam is very little, and if the cancer is more than 5 mm. in thickness either supplementary interstitial irradiation should be employed or the radon or radium tubes should be implanted more deeply into the moulage, to give a greater intervening distance and a correspondingly better depth dosage. Regardless of histologic grading, the dose selected is usually the one capable of sterilizing the most radioresistant epidermoid carcinoma with preservation of the normal tissues. Radium moulages are especially desirable for superficial cancers about the ear, nose and lip.

Radon Seeds.—Radium may be placed in solution (as chlorides), and the radon gas emanating is pumped off by means of a Failla radon apparatus into small capillary tubes having a wall of gold 0.3 mm. thick. Gold radon seeds for interstitial irradiation are 4 mm. long and usually contain 1.2 to 3 millicuries per seed. They remain permanently in the tumor long after the radon has been completely dissipated.

Gold radon seeds are indicated in the treatment of small recurrent cancers or whenever interstitial radon is desired as an adjunct to contact or short distance radium therapy by moulage or plaque. Their chief value is in the treatment of small cutaneous cancers of the ear, eyelid or face. They should not be inserted too near cartilage or a painful and chronic perichondritis may follow.

Radon Bulb.—Radon in the quantity of 300 to 600 millicuries is collected at intervals and pumped into a tiny glass sphere embedded in a wax cup at the end of a long handle. This glass radon sphere is placed in direct contact with lesions of the skin to give doses varying from 200 to 600 millicurie minutes. This method of employing radium is limited to precancerous lesions, particularly keratoses, and to very small and superficial basal cell epitheliomas, less than 2 mm. in thickness.

SURGICAL TREATMENT OF EPITHELIOMAS OF THE SKIN

The procedure of choice for cancers at different locations will be considered later. Since the surgical technic varies with the anatomic location of the tumor, no attempt will be made to discuss this in general.

A few brief comments will suffice to bring out the important points in this method of approach.

The line of excision should be carried well beyond the palpable margins of the tumor. Deep incisions should be so directed as to avoid injury to important nerves and blood vessels. If immediate skin grafting or transplanting is planned, a sharp scalpel should be used. No hard and fast rule can be laid down; the location and nature of the cancer determine the operative technic. Endotherm excision, with or without preliminary coagulation of the cancer, may be carried out if immediate skin grafting is not planned. This technic is especially adapted for vascular large recurrent cancers.

Amputation is indicated in the following circumstances: (1) when the cancer has invaded so deeply and become so adherent that excision is an impossibility; (2) when the interior of a large articulation, such as the knee or ankle, is extensively laid open; (3) when large areas of bone are exposed, a condition which results in necrosis; (4) when profound and uncontrollable suppuration of the wound is complicated by fever and a dangerous toxemia and (5) when the functional result, even after a presumptive local cure, would be unsatisfactory, the limb becoming an encumbrance.

FACTORS INFLUENCING THE CHOICE OF TREATMENT

1. *Location of the Cancer.*—A cancer in close proximity to bone or cartilage should be treated by surgical intervention, as heavy irradiation may cause a perichondritis, periostitis or osteitis, which may slough and remain painful for many months. This would include epitheliomas located on the dorsum of the hand or foot, anterior tibial region, midline of the back, midsternal region and scalp. On the other hand, surgical excision of epitheliomas involving the eyelids, nose, ear, external auditory meatus and penis may sacrifice organs and tissues which are difficult to restore by plastic reconstruction. Radiation therapy is the method of choice provided the tissues are not involved by cancers too deeply infiltrating and destructive to be amenable to conservative irradiation.

Eyelids: While irradiation is preferable to surgical excision for epitheliomas of the eyelids, it is important to consider the advantages and disadvantages of the various types of irradiation available. The dangers to the eye from irradiation are two: late cataract and iridocyclitis which may terminate in glaucoma. When low voltage roentgen rays are directed through small cones to the epithelioma and the eyeball is protected by a small lead shield inserted in the conjunctival sac, the lens receives practically none of the dose delivered to the tumor. Thus this becomes the method of choice in this location for these reasons: (1) the general availability of roentgen therapy, (2) the

avoidance of late sequelae, such as cataract, and (3) the difficulty in shielding the eyeball when radium plaques are used.

Nose: The majority of tumors of the nose are of the basal cell type and respond with good results to radiation therapy. Low voltage roentgen ray therapy is preferred, but radium plaques give successful results. It is imperative that the dose be calculated carefully, in order that a perichondritis and chondritis with the possible result of a painful ulcer may be avoided. The actual cautery or endotherm knife is indicated when the cartilage is deeply invaded.

Ear and Auditory Canal: Radiation therapy is indicated, unless the cartilage is largely destroyed. Low voltage roentgen rays or contact radium therapy by means of a moulage are equally successful. The superficial insertion of gold radon seeds is used for cancers of the external auditory meatus.

Hands and Feet: The skin over bony prominences is usually poorly nourished, and for this reason irradiation is not indicated. The only possible exception occurs when the epithelioma of the dorsum of a hand or foot is superficial and not of great thickness. Radium plaque treatment or low voltage roentgen therapy administered in fractional daily doses by the Coutard technic is preferable. Cancers of the sole, especially the heel, are usually treated by surgical excision. After irradiation the skin will not tolerate injuries or weight bearing. If muscles, tendons or bone are involved, partial amputation of the hand, foot, finger or toe may be necessary.

Scalp: Some of the epitheliomas are of the basal cell type; others are squamous cell carcinomas, some of which originate in sebaceous cysts. Although the scalp is highly vascular and should support irradiation well, late radionecrosis or later recurrence often follows radiation therapy. If the epithelioma is at all evasive, wide excision by electrocautery down to the pericranium is the treatment of choice. Involvement of the pericranium calls for sacrifice of this structure and perhaps of the outer plate of the calvarium.

2. *Type and Stage of Cancer.*—The basal cell epitheliomas of the skin grow slowly and, because of their long duration, are usually detected early, while they are still superficial and before they have attained great size. Irradiation can be used for the ordinary small ulcerating tumors of this type, with the radium plaque as the method of choice. On the other hand, the basal cell tumors which contain mucin and have a decided adenoid appearance (adenoid cystic epithelioma) are radioresistant.

The factors of fixation and infiltration are more important than the histologic grading in the radiosensitivity of epidermoid carcinoma. This tumor grows more rapidly than the basal cell carcinoma. Spindle cell metaplasia of epidermoid carcinoma increases the radioresistance

to a degree wherein the cancer will remain viable, even though the normal surrounding tissues will slough from overirradiation.

A papillary carcinoma covering extensive areas should be removed in part by surgical endothermy, with irradiation being applied to the base. If the epithelioma occupies a large surface area, fractional roentgen ray therapy is preferred to a massive single dose. If the lesion exceeds 6 cm. in diameter, a single treatment of 4,000 r should not be given. Protracted fractionization of the dose is desirable if the cancer is infiltrating deeply.

Irradiation is contraindicated in the presence of fixation, e. g., in squamous cell carcinoma of the dorsum of the hand. Invasion of the bone by contiguity is extremely radioresistant, and surgical excision is indicated. The adenoid cystic type of basal cell carcinoma has a tendency to involve bone.

3. *Treatment of Recurrent Cutaneous Cancers.*—When a cancer of the skin recurs after irradiation, as a rule further irradiation is not indicated. There is a loss of the original radiosensitivity, and a larger dose of irradiation would be required. At the same time the normal adjacent tissues are more prone to radiation ulceration. The location of the cancer, the amount of previous irradiation and the histologic type of the cancer must be taken into account before one may arrive at a decision for further treatment by this means. If the recurrence occupies only a small proportion of the original cancer, it may be treated by gold radon seeds or external irradiation with the healed area protected by lead. In the presence of spindle cell metaplasia, surgical excision is imperative.

Cancers recurrent after incomplete excision do not respond to irradiation, as the cells are growing in scar tissue and the tumor is deep in or beneath the skin. In some instances, however, gold radon seeds have been inserted at intervals of 1 cm. along the line of incision or into the recurrent tumor if it is palpable.

4. *Selection of Treatment of Cancers of Certain Types and Origins.*—The method of choice will be presented for some of the commoner types of cancer with which many surgeons have to deal.

Bowen's Disease: This tumor should be considered a true carcinoma, and the treatment should be the same as for squamous cell carcinoma.

Paget's Disease: While this lesion appears on the skin, it is associated with deeper tumors in the ductal system of the breast. For this reason it should be treated as carcinoma of the breast, with amputation.

Cancer in Acrodermatitis Chronica Atrophicans: Irradiation frequently results in immediate or late ulceration, and wide surgical excision followed by skin grafting is the method of choice.

Cancer in Xeroderma Pigmentosum: The use of roentgen rays and radium has no place in the treatment of this disease. Excision by knife or endotherm or coagulation by diathermy or cautery should be undertaken.

Cancer in Lupus Vulgaris and Lupus Erythematosus: In many instances the patients have received previous low voltage roentgen ray therapy for lupus, and the epitheliomas developing later are essentially scar tissue, which may not tolerate a cancericidal dose of irradiation. Wide surgical excision with plastic repair may be necessary.

Arsenical Cancer: The epitheliomas which develop on these precancerous lesions may be either squamous cell or basal cell in type, slowly growing, somewhat radioresistant and metastasizing late to regional lymph nodes. Because of their superficial nature in the majority of cases, they are usually treated by the application of radium plaques. Low voltage unfiltered and lightly filtered roentgen rays are also suitable for treatment either with the 100 kilovolt machine or with the Chaoul or Philips short distance outfits. When these lesions develop on the palms or soles, they often respond to irradiation but late necrosis may develop. This requires surgical excision, with considerable disability over a long period. The current trend in the treatment of this type of cancer is toward wide and deep surgical excision followed by immediate whole thickness skin grafts.

Cancer in Chronic Radiation Dermatitis: These cancers are notoriously radioresistant. They are usually squamous cell carcinomas, occasionally exhibiting a spindle cell metaplasia, with a high degree of malignancy. They metastasize relatively early to regional lymph nodes. The proper treatment is either wide surgical excision with immediate application of whole thickness skin grafts or electrocoagulation followed by endotherm excision and secondary skin grafting.

Cancer in Burn Scars: These cancers are slowly growing radioresistant neoplasms, almost invariably of the squamous cell type. Wide radical excision followed by skin grafting is the treatment of choice.

All scar tissue is intolerant of irradiation, which presents the following difficulties: 1. The squamous cell cancers originating in scars are highly differentiated, adult, radioresistant neoplasms. 2. Owing to insufficient blood supply, the normal process of repair of the tissue reaction following irradiation is weak or absent in the scar bed. 3. The constant infection of these ulcers interferes with successful irradiation. 4. Radionecrosis and sloughing occur quickly and with relatively low doses. When irradiation is unsuccessfully employed, it makes the base of the ulcer more fibrotic than ever and impairs healing. In such an event, the radiation therapy should be followed by wide excision and skin grafting.

Cancer in Draining Sinuses: Osteomyelitic, tuberculous or operative sinuses of long duration are sources of chronic irritation in which cancers, usually of the squamous cell type, not infrequently develop. The first problem is to eradicate the cause of the sinus if possible, and wide surgical or endotherm excision offers the only hope. In some instances, external and interstitial irradiation have been successful. Although essentially a scar cancer, the growth is usually papillary and somewhat radiosensitive. The divided dose technic rather than massive roentgen ray therapy gives better results. If gold radon seeds are used, they are inserted through the normal surrounding skin. Even after successful radiation, treatment débridement is often necessary.

5. *Treatment of Metastatic Carcinoma in Regional Lymph Nodes.*—Indications for Dissection of Regional Lymph Nodes: The regional lymph nodes are never molested unless there is clinical evidence of their involvement by metastatic cancer. Aspiration biopsy of a lymph node may reveal carcinoma and thus establish the indication for treatment; a negative report following aspiration biopsy of a lymph node does not rule out the presence of metastases. The enlarged lymph nodes may subside if the infection in the primary cancer is controlled by hot antiseptic dressings but never if metastases are present. It is a safe rule to suspect all enlarged regional nodes of containing metastatic carcinoma until proved otherwise.

Surgical Treatment: The dissection of cervical or inguinal nodes should be complete. This dissection never precedes the treatment of the primary cancer and is seldom done at the same time. The usual procedure is to treat the primary cancer first by surgical excision or radiation therapy; when the wound has healed or the irradiated cancer exhibits satisfactory regression, the dissection of the lymph node–bearing region is performed. The interval between these procedures varies from one to three weeks.

Radiation Therapy: Metastatic squamous cell or spindle cell carcinoma cannot be cured by irradiation alone. If the diagnosis has been proved by aspiration of the enlarged nodes or if the presence of metastases in the nodes is strongly suspected, radical dissection followed by postoperative irradiation is the method of choice. Such radiation therapy is given prophylactically, not with the hope of sterilizing residual cancer but to induce fibrosis in these tissues, prevent the reformation of new lymphatic channels and possibly exercise a restraint on the growth of any viable cancer left after the dissection.

Individual cervical nodes containing metastatic carcinoma, if inoperable or occurring in patients unsuitable for operation, may be treated by external irradiation with the protracted divided dose technic. The roentgen rays are applied with the following factors: 200 kilovolts;

0.5 mm. copper and 1 mm. aluminum filtrations; 50 cm. target-skin distance; circular ports through cones to encompass the involved nodes only and daily fractional doses of 200 to 300 r until each port has received from 2,000 to 3,600 r units.

After the completion of external irradiation, supplementary interstitial radiation therapy may be used by the insertion of gold radon seeds in measured tissue doses. This treatment is more successful for cervical nodes containing metastatic carcinoma, because these nodes have strong capsules which restrain the carcinoma within the node. The axillary and inguinal nodes have delicate capsules often infiltrated by fat; metastatic cancers in these nodes may perforate the capsule early and invade the loose fat of the axilla or groin, thus defeating most attempts at control by irradiation. The involved lymph nodes, especially in the cervical group, are exposed through a limited incision so that one may implant the radon seeds or small radium needles with greater accuracy.

CUTANEOUS CANCER FROM THE POINT OF VIEW OF THE RADIOLOGIST

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THE indication for type of treatment in cancer of the skin will depend on the following factors: age, life expectancy, location, occupation, invasion of bone and cartilage, previous treatment, nature of the tumor bed and previous trauma and its presence in scars.

Regardless of the type of neoplasm, in very aged persons and others whose life expectancy is short, cure is often sacrificed for palliative effect. Therefore, for many patients for whom surgical excision rather than radiotherapy might be indicated, the latter treatment would be the method used.

Carcinomas of the scalp or the extremities are usually treated better by surgical means. This is especially true for those of the feet and in the pretibial regions. Radiotherapy for young patients should not be used on parts of the body where there will be constant irritation or on exposed parts, such as the face and more especially the ears, which will be exposed to extremes of weather, especially cold and intense sunlight.

Cancer resulting from roentgen ray burns and cancer in scars from other burns do not as a rule do well with radiation therapy. However, numerous small lesions, less than 1 cm. in diameter, can be successfully eradicated by radiotherapy. The results with radium therapy have not been uniformly good, especially in the early days before the establishment of the gamma "r" unit of measure. It has been found that roentgen rays are more easily applied and that the results are superior. This has been borne out in an experience of over 300 cases of cancer involving all parts of the body and of both squamous cell and basal cell types. It has been found that everything else being equal it is no more difficult to eradicate a primary tumor if it is a squamous cell than if it is a basal cell cancer

The management of metastatic lymph nodes is mainly a surgical problem. However in cases in which this is contraindicated, long

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palliation and a possible cure may be obtained by radiologic means (roentgen rays and intrinsic radon implantation).

For lesions 0.5 cm. in diameter or smaller, a single treatment of 3,000 or 3,600 r is used. For larger lesions up to 3 cm. in diameter the dose is five times 900 r (80 to 100 kilovolts) given within ten days. When contact therapy is used (45 kilovolts, filter of 1.2 mm. of aluminum and focus-skin distance 4.1 cm.), six times 1,000 r is the dose. With this technic the rate of cure among patients with primary tumors not previously treated was over 90 per cent.

It has been found in general that invasion of cartilage is not a contraindication to radiotherapy unless the patient is exposed to extremes of temperature and sunlight, which may bring about the breakdown of the scar at the site of the treated lesion. There is no advantage in electrocoagulation or desiccation of the lesion before roentgen ray therapy. A careful setup with the use of lead cut-outs over the lesion allowing a minimum of 0.5 cm. of healthy tissue around small lesions and larger areas of healthy tissue around larger lesions has been found to be a practical necessity for a high percentage of cure.

RADIOTHERAPY OF EPITHELIOMA OF THE SKIN *

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THE treatment of epithelioma of the skin by roentgen rays and radium is influenced by the accessibility of the growth to irradiation, by its radiosensitivity (as contrasted with the radioresistance of the normal tissues included in the irradiated field) and, finally, by the dosage and the technic of radiotherapy.

ACCESSIBILITY

Ninety-eight per cent of the basal cell and 75 per cent of the squamous cell epitheliomas of the skin are located on the head or neck, while 2 per cent of the basal cell and 25 per cent of the squamous cell cancers are found on the trunk and extremities. Basal cell epitheliomas usually grow slowly, often remain flat and show central excavation, and, except in certain locations, they rarely invade subjacent tissues and do not metastasize to regional nodes. Squamous cell epitheliomas are more likely to proliferate without undergoing necrosis, to form bulky growths or to invade and they metastasize in about 18 per cent of the cases.

Because most epitheliomas of the skin are treated while they are still small and accessible, all types of therapeutic procedures are often successful. Curability decreases with increasing size of the growth on the surface, especially if the epithelioma tends to invade subjacent tissues or to metastasize.

"Invasive" epitheliomas are more likely to have silent extensions and if they are squamous to have regional metastases. A special tendency to invasive growth of basal cell epitheliomas is noted if they are located at the inner canthus of the eyelids or at the edge of the nostril and if they are located on the forehead, a site more common in women. Squamous cell epitheliomas with invasive tendencies are found on the pinna of the ear (mostly in men), in the external auditory canal (chiefly in women), on the dorsum of the hand and at mucocutaneous junctions, e. g., the lower lip, the anus, the vulva and the penis.

* At the request of the editor, all references have been omitted for the sake of brevity.

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Accessibility and radiocurability depend on the location, the extent on the surface and, more especially, the depth of the primary growth as well as the presence or absence of involvement of regional lymph nodes.

RADIOSENSITIVITY OF TUMOR

The second factor governing radiocurability is the inherent radiosensitivity, i. e., the immediate response of the tumor as contrasted with the radioresistance of the normal tissues included in the irradiated field. The importance of this factor is best appreciated in the treatment of extensive epitheliomas, as small epitheliomas are frequently overradiated and destroyed, irrespective of their inherent radiosensitivity. Basal cell epitheliomas may regress with a slightly smaller dosage of radiation than that needed for well differentiated squamous cell growths of the same extent. Some poorly differentiated squamous cell epitheliomas, however, regress as readily as do basal cell tumors, e. g., bulky epitheliomas developing in sebaceous glands in the preauricular or masseteric regions. More radioresistant and preferably not treated by radiotherapy but by excision are the rare adenocarcinomas and adenocystic epitheliomas arising in sweat glands. In exceptional circumstances, however, radiotherapy may be preferable to operation, or vice versa, in cases in which this treatment ordinarily would not be employed.

RADIORESISTANCE OF TUMOR BED

The normal tissues included in the field of irradiation are exposed to the same dose of radiation as the tumor. Whenever possible, therefore, radiosensitive normal tissues should be excluded from the irradiated field. For instance, in roentgen ray therapy of epitheliomas of the eyelids, the globe is protected by inserting lead shields under the lids. Special lead shields are used to shield the testes when epitheliomas of the skin of the scrotum are irradiated. If such shielding is impractical, the radiosensitivity of the irradiated normal tissues limits the dose which may be administered to the tumor and influences the technic of radiotherapy.

Retrogressive radiation changes of all irradiated tissues normally follow intensive radiotherapy. Injury of the capillary layer at the edge of the rete pegs, i. e., about 1 mm. below the surface, probably accounts for erythema, exudation, depigmentation and telangiectasia which follow irradiation. Edema, folliculitis and late radionecrosis may represent damage of the coarser capillary layer at the limit of the subcutis, or about 2 mm. below the surface. Epilation suggests an effect of radiation at the level of the hair follicles 2 to 3 mm. below the surface.

Radiation damage of the tumor and of the normal tissues included in the field of irradiation is proportional to the amount of irradiation and is in inverse proportion to the duration of the treatment: The shorter the treatment, the greater is the damage, provided the total amount of irradiation is the same. The difference in the threshold of radiosensitivity of the tumor and the tumor bed is reduced if the treatment is intensive and short; if, in addition, the dosage is slightly excessive, destruction of the epithelioma may be followed by atrophy and telangiectasia of the irradiated skin. The time when radiation damage becomes clinically appreciable depends on the normal life cycle of the irradiated cells and the intensity of the radiation dose: The larger the radiation dose or the shorter the natural life cycle of the irradiated tissue, the sooner will the radiation damage be recognizable. Thus, intensively irradiated short-lived epithelium of the skin and, more especially, of mucous membranes, will die and desquamate within a few days or weeks after the exposure. Similarly, irradiated long-lived connective tissue or bone may not show any radiation damage for months or even years following the treatment. Dilatation of capillaries with consequent erythema may be seen early after a moderate radiation dosage. With more intensive irradiation, greater dilatation and even rupture of capillaries with interstitial hemorrhage may occur soon after irradiation. Telangiectasia, obliterative endarteritis and hyalinization of the connective tissue take time to develop and may not appear for months or even years after radiotherapy has been completed.

Poorly vascularized skin and subcutaneous tissues do not tolerate intensive radiotherapy well. The interference with the blood supply may have been produced by preceding disease, surgical trauma, intensive radiotherapy or other causes. If vigorously irradiated, this sclerotic tissue may undergo necrosis, as its blood supply is further decreased by the intensive irradiation. This partially explains the poor results of treatment with roentgen rays and radium of lupus, carcinoma, epitheliomas arising on the basis of old chemical or heat burns, most of which are well differentiated, and of scar epitheliomas of all kinds; it partly accounts for the failure of repeated radiotherapy for cancer in which preceding radiation has failed. Surgical treatment is preferable to radiotherapy in most of these cases.

Cartilage or bone adjacent to an ulcerating epithelioma receiving cancericidal doses of radiation may be damaged by irradiation, and chondritis, osteitis or even chondronecrosis or osteonecrosis may develop. This is more likely in such sites as the pinna, nose, chin, forehead and scalp, in which there is little protective soft tissue between the perichondrium or periosteum and the irradiated skin. Occasionally epitheliomas invading the pinna or ala nasi have been cured by irradiation, and those which have not invaded the perichondrium or periosteum

are as curable by radiotherapy as epitheliomas in other portions of the body. The likelihood of radiation damage is increased if the tolerance of the cartilage or bone has been previously impaired by the entrance of bacteria, invasion by epithelioma or interference with the blood supply due to previous operation or radiotherapy. Because of this fact, it is usually better to remove surgically epitheliomas invading cartilage or bone and to exercise special caution if radiotherapy is applied.

Infection, except in persons with uncontrolled diabetes, is not usually a serious problem in radiotherapy of epitheliomas of the skin. Ordinarily the infection is on the surface and disappears with the radiation slough of the tumor. Rarely a streptococcic or staphylococcic cellulitis or lymphangitis has to be cleared up before radiotherapy of the epithelioma is started.

METASTASES TO LYMPH NODES

The presence of metastases to lymph nodes from squamous cell epithelioma of the skin reduces the likelihood of a five year cure from the accepted figure of 54 per cent (without nodes) to 18 per cent (with nodes). Radical surgical treatment is preferable if the nodes are freely movable, small and only few in number. Radiation is better if the nodes are multiple or fixed. Roentgen ray therapy, insertion of seeds or radium or radon needles with or without surgical exposure or the use of teleradium has at times been successful, but more often is only of temporary value.

TECHNIC

The technic of the treatment of epithelioma of the skin with roentgen rays and radium is greatly influenced by a consideration of the various factors just discussed. For instance, the extent of the epithelioma on the surface and, more especially, its invasiveness have a bearing on the size of the irradiated field, the target-skin distance and the filter, on the daily and total dosage, on the period of treatment and, finally, on the voltage if roentgen ray therapy is used. The radioresistance of the tumor bed, especially its blood supply, influences the daily and total dosage and the period and repetition of the treatment. Finally, such considerations as the general tolerance and life expectancy of the patient must be taken into account in planning the treatment.

Decision as to whether to choose radium, its emanation gas, radon, or roentgen ray therapy depends on what available source of radiation is best suited for the special location and extent of the epithelioma.

Radium Therapy.—Radium may be used externally or interstitially. Radon may be substituted for the parent element provided its natural 16 per cent daily decay is taken into account.

In external radium therapy there are used special felt, rubber or wax applicators, which may be accurately molded to the outlines of the individual epithelioma, or ready plaques, trays and other applicators of fixed

shape and form, not adapted as precisely but nevertheless satisfactory for some epitheliomas which happen to fit the shape of the applicator. Applicators made of Columbia paste (paraffin, yellow wax and wood shavings) or those of dental modeling compound (Kerr) are molded while hot over the part to be treated; they are soft and pliable when heated and become hard and rigid when cooled. If it is practical, it is advantageous to include a bony prominence, e. g., the nose or jaw, so as to prevent shifting of the mold during treatment. Tubes containing 5 to 10 mg. of radium element or corresponding quantities of radon, filtered through 1 mm. of platinum or its equivalent, are distributed on the outside of the mold in accordance with accepted physical rules of the distribution of radiation. The mold is left on for the desired period and then removed.

In a few institutions, 2 to 10 Gm. of radium element or its equivalent in radon have been concentrated in large, usually lead-lined, steel containers, called "packs" or "bombs." They have a diaphragmed opening through which the radiation beam is directed, like that of an x-ray tube. This type of teleradium therapy is useful in the treatment of metastases to lymph nodes and occasionally for deeply invasive epitheliomas.

For interstitial irradiation either needles or seeds are employed. The short active length of the gold or platinum seed (0.5 cm) limits its usefulness chiefly to superficial lesions in which homogeneous distribution of radiation throughout the thickness of the tumor is relatively easy; for deeper epitheliomas needles are preferable, as their radiating length may be varied from 1 to 5 cm., according to the thickness of the tumor. Seeds are usually filled with 1 to 2 millicuries of radon, whereas needles contain per centimeter of radiating length anywhere from 0.5 to 10 mg. of radium element or a corresponding quantity of radon. Needles have to be removed after the desired period of irradiation; seeds may be abandoned in the tissues, as the radon becomes practically inactive in a month and the seed either sloughs through the surface or becomes encapsulated like any foreign body.

Seeds or needles of appropriate length are inserted into the tissue 1 cm. apart. In small lesions they are inserted chiefly into the periphery of the tumor. In extensive epitheliomas additional needles or seeds are inserted into the center of the neoplasm. Allowance must be made for the poorer nourishment of the center of the neoplasm, as well as for the effect of the cross firing when irradiating with multiple needles or seeds, in accordance with standard physical rules for the distribution of radiation.

The Field.—In order to include possible silent extensions at the periphery of the epithelioma, the irradiated field should extend beyond the clinical limits of the growth. Multiple biopsies beyond these limits

may reveal much wider invasion and thus prevent failure of treatment, especially in extensive and in massive epitheliomas. If roentgen ray therapy is used, the width of the zone of apparently normal skin surrounding the cancer should be 0.75 cm. for epitheliomas which are less than 2 cm. in diameter. It should be widened to 2 or 3 cm. and in exceptionally large epitheliomas even to 5 cm., depending on the increasing extent of the epithelioma on the surface and especially on its tendency to invade subjacent tissues. Invasive epitheliomas may show a tiny surface tumor and a wide subsurface extension, like a submerged iceberg.

If radium is used, one should follow the same general principles.

Target-Skin Distance.—In contact roentgen ray therapy of very superficial epitheliomas, the usual target-skin distance is 1.8 to 4.1 cm. For deeper epitheliomas a distance of 15 cm. for fields of diameters of 5 cm. and less and of 30 cm. for larger fields is recommended if 100 to 135 kilovolts is used. For extensive invasive lesions, a target-skin distance of 50 cm. and 130 to 200 kilovolts are usually preferred. The target-skin distance for fungating lesions should be measured from the level of the skin and not from the top of the fungating neoplasm. The fungating part of the neoplasm is thus overirradiated without similar damage to the skin. A hollow radiation cone into which the mass fits facilitates this type of roentgen ray therapy.

In external radium therapy of small noninvasive epitheliomas, the usual target-skin distance is 0.7 to 1 cm. This may be increased up to 3 cm. for the more infiltrating types of growth. In teleradium therapy, target-skin distances of 6 to 14 cm. are employed.

Filter.—Roentgen ray therapy of superficial lesions with 45 to 100 kilovolts is given without a filter or with one of 1 mm. of aluminum; for more invasive epitheliomas, 3 mm. of aluminum and 130 kilovolts, and for those penetrating still deeper, 0.5 mm. of copper and 200 kilovolts are commonly used.

The standard filters for radium have usually been of 1 mm. of platinum or its equivalent for radium tubes, 0.5 mm. of platinum for radium needles and 0.3 mm. of gold for gold seeds.

Voltage.—Most epitheliomas of the skin do not penetrate deeper than the first centimeter, and only few extend beyond 3 cm. below the surface. If 45 kilovolts, a 2 cm. field and 4.5 cm. target-skin distance are used, the depth dose at 0.5 cm. is 40 per cent and at 1 cm. 23 per cent. With roentgen rays of 50 to 60 kilovolts, that is, 0.9 angstrom, 87 per cent of the radiation is absorbed within the first centimeter of tissue. Most epitheliomas of the skin are probably still treated with voltages of about 100 kilovolts, though for the more invasive types 130 or 200 kilovolts is preferred.

Repetition of Treatment.—If one hopes to cure an epithelioma, a single irradiation treatment is given. This first and only treatment may consist of one exposure or of a series of exposures, but once completed it is never repeated unless the epithelioma has persisted or has recurred. This is done so as to avoid reirradiating previously treated normal tissues forming the tumor bed. The retrogressive radiation changes in normal tissues occurring after intensive radiotherapy have been discussed under the heading of "Radioresistance of the Tumor Bed." If a cure is not expected, weak radiation intensities are repeated from time to time in order to restrain growth and relieve symptoms. Repetition of such sublethal noncancericidal doses every few weeks or months, however, does not destroy cancer completely. The cancer cells which are not killed reproduce between treatments and present a front of fresh, undamaged daughter cells when the growth is again irradiated. The blood vessels and connective tissue of the tumor bed, on the other hand, are not replaced by new ones but cumulate the damage of each successive exposure and finally succumb, undergoing radionecrosis. In attempts at curative radiotherapy, all treatment is therefore completed before noticeable retrogressive radiation changes have taken place in the irradiated blood vessels and connective tissue, i. e. within two or two and a half months. These normal structures, then, are able to tolerate the damage of this first and only series of intensive radiotherpy.

Criterion of Adequate Dosage.—A cancericidal dose for each variety of epithelioma has as yet not been accurately determined. For all epitheliomas it is therefore cutomary to administer a radiation dose which will destroy the epithelium from which the epithelioma originated and yet allow the corium to live, so as to permit reepithelization of the denuded area of skin. Irrespective of the technic of irradiation, correct irradiation should produce a complete wet desquamation of the irradiated epidermis, leaving under it a denuded, raw bleeding corium. Healing after denudation occurs by ingrowth of epithelium from the edges just outside the irradiated field and from a few epithelial cells in the depths of the hair follicles, which escaped destruction by the radiotherapy. The speed with which healing takes place depends on the size of the denuded area which has to be covered and the radiation damage to the underlying blood vessels. Healing is prompt in small areas and slower in larger ones and may take from one to several weeks. Epithelization may be slow or even inadequate to cover the defect if the amount of irradiation has been too great, if it was given in too short a time, if the field has been too large or if the nourishment of the normal tissues included in the irradiated field has become impaired. In extreme circumstances pinch or even pedicle grafts are needed to cover the nonhealing denuded area. Epitheliomas have been cured with lower dosage and without wet desquamation, yet I should not like to recommend this method.

On the other hand, wet desquamation only denotes adequate dosage at the level of the desquamation and gives only indirect information as to the sufficiency of radiation below this level. Though the threshold of the radiation dose which will produce a wet desquamation is narrower and therefore more reliable than that which will cause an erythema, it indicates only the minimal and not the maximal dosage which has produced this reaction.

Massive Versus Fractional Radiotherapy.—Decision as to whether to administer the entire dose in one exposure or to fractionate it into several treatments depends on the size and vascularization of the irradiated area. The shorter the period of treatment, the greater the effect on the tumor, but also the more damaged are the blood vessels and the connective and other normal tissues included in the irradiated field. If one administers the entire dose in one massive exposure, there is less difference in the injury to the tumor and tumor bed than if this dose is fractionated. In this form of radiotherapy, destruction of the epithelioma may be accompanied by destruction of the normal tissue included in the field of irradiation. Massive therapy is therefore confined to small fields located in nonvital areas and may be used for the average superficial basal cell epithelioma 1 to 2 cm. or less in diameter. Fractional radium or roentgen ray therapy may be as effective in the treatment of cancer as massive therapy is, yet it spares the normal tissue more. It is preferable to the massive method of treatment when the tolerance of the tumor bed is low, the field to be irradiated is large and repetition of exposures is not inconvenient to the patient. Fractional therapy would be chosen for treatment of epitheliomas near cartilage, as massive therapy would be more likely to cause chondronecrosis.

Total and Daily Dosage.—Dosages vary in different clinics. The total dose is increased if the size of the field is made smaller. With contact roentgen ray therapy in so-called "caustic irradiation," single doses of from 6,000 to 12,000 r have been administered and good healing has resulted. Three thousand roentgens with 100 kilovolts, 15 cm. target-skin distance and no filter (half-value layer-1 mm. of aluminum) for basal cell epitheliomas 1 cm. in diameter has yielded satisfactory results. A total dose of 4,000 to 6,000 r, depending on the size of the field, fractionated into daily dosages of 250 or 500 r every other day leaves a better scar and may be more effective. With 130 and 200 kilovolts, smaller daily and total doses are needed, in view of the greater volume of irradiated tissue and the increased scattered irradiation.

With external radium mold therapy at 0.7 cm. target-skin distance, 1,000 milligram hours and a filter of 1 mm. of platinum to a 2 by 2 cm. field used to be a standard dosage. Nowdays 4,500 to 7,000 r of gamma radiation is usually given to fields of various sizes.

Teleradium dosage varies with the target-skin distance and the size of the field. In interstitial therapy, 1 millicurie destroyed or 133 milligram hours per cubic centimeter of tissue was formerly the standard. Nowadays one attempts to obtain in from five to ten days a tumor dosage of 4,000 to 6,000 r of gamma rays for basal cell epitheliomas and from 6,000 to 7,000 r for squamous cell epitheliomas.

Operation or Radiotherapy.—Decision as to whether a particular epithelioma should be treated by radiotherapy, electrocoagulation, application of zinc chloride or excision depends on the experience and skill of the person making the decision, on the availability of the proper equipment and on the extent and location of the epithelioma. Radiotherapy might be preferable for parts of the body where resection and plastic repair would be deforming, e. g. on the nose. Surgical treatment would be better than radiotherapy in most cases with invasion of fibrous tissue, bone or cartilage, e. g., in deep or extensive epitheliomas of the scalp, auricle, etc. It would be preferable where the tumor bed is poorly nourished, e. g. in epitheliomas on the basis of an old lupus or a burn or after failure of radiotherapy, especially if telangiectasia and atrophy are present. Electrocoagulation might be chosen as a palliative measure in the treatment of an inoperable lesion recurring after radiotherapy. As far as curability of the average epithelioma is concerned, it is immaterial whether one uses radiotherapy or surgical intervention provided adequate treatment is applied to all cancer cells. Success depends on the appreciation of the extent of the growth and its adequate treatment during the first and only treatment.

SUMMARY

The use of roentgen ray and radium or radon for the treatment of epithelioma of the skin is influenced by the accessibility of the growth to irradiation, by its radiosensitivity as contrasted with the radioresistance of the tumor bed and, finally, by the dosage and technic of radiotherapy as discussed in the preceding pages.

GROSS PATHOLOGY OF CUTANEOUS CANCER

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IN THIS brief survey, the biologic characteristics of the principal malignant epithelial neoplasms of the skin will be presented from the point of view of gross morphology and its importance in diagnosis, prognosis and treatment. Melanomas will be excluded, and the group to be considered will consist of basal cell and squamous cell epitheliomas, including Bowen's disease, and carcinomas of sweat and sebaceous glands. An idea of the relative frequency of these tumors may be gained when it is stated that during a ten year period there were recorded in the laboratory 1,224 malignant tumors of the skin—605 of these were basal cell cancers; 309 were squamous cell tumors, including Bowen's disease; 21 were sweat gland carcinomas, and 2 were sebaceous gland cancers. The remainder consisted of 150 malignant melanomas, 55 sarcomas and 82 secondary neoplasms.

In order to obtain a broad general view of cancer, one should visualize it as starting from a focal point or occasionally from several focal points and growing centrifugally in all directions. For some reason not understood, the growth and spread does not take place at an equal rate in all directions in every tumor but tends to expend its chief growth energy in one of three different directions. For the skin these are: first, outward from the body surface and at right angles to it, producing a projection; second, in the exact opposite direction—that is penetrating inward into underlying tissues producing early ulceration—and, third, parallel with the body surface, either within the epidermis alone or involving both epidermis and papillary layers. There are, of course, exceptions in which a tumor may display two or even all three of these growth characteristics in equal degree, but the majority can be so divided.

These features account for the gross appearance of the tumors and have some bearing on their treatment and prognosis. Of the squamous cell cancers, the deeply penetrating ulcerating tumors are most often seen in irradiated and other scarred areas while the spreading superficial

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tumors include Bowen's disease and other intraepidermal epitheliomas. In the case of basal cell cancer, the deeply infiltrating tumors are the rodent ulcers and the superficial spreading ones are the multicentric basal cell epitheliomas and self-cicatrizing "field fire" tumors. Of the much rarer sweat gland and sebaceous gland carcinomas, examples of the spreading form have not been described. Many of the tumors are projecting, a few infiltrating and some a combination of the two.

In general, one can say that as a group the infiltrating tumors are the most malignant and hardest to eradicate. The projecting tumors are much less malignant and much easier to cure because of the absence of deep penetration. The superficially spreading tumors are also less malignant and present no difficulties so far as deep penetration is concerned. The question of metastasis seldom arises, except in the case of squamous cell epithelioma. Here the rule holds, for it is the deeply penetrating ulcerated squamous cell tumors which most frequently metastasize. Metastases from basal cell epitheliomas and sweat gland and sebaceous gland carcinomas are so rare that no generalization about them is permissible. There are records of two examples of metastasis in each of these three types of tumor in the laboratory of surgical pathology of Columbia University. Most of them occurred in tumors which both projected and infiltrated.

It must be emphasized that this statement is not intended to express an inflexible rule but is simply a possibly useful generalization about the growth tendencies of these malignant tumors.

HISTOPATHOLOGY OF CUTANEOUS CANCER

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IN a brief review of a large subject, only the important features can be enumerated with little or no explanation of many others being made. Therefore, I believe, I need not consider the adnexal neoplasms, as syringoma, trichoepithelioma, multiple benign cystic epithelioma and the others. These are either nevi or nevoid lesions and are not malignant.

Epitheliomas of the skin are epithelial neoplasms which are malignant. There are three large groups, depending on the cells involved: basal cell, prickle cell and undifferentiated cell. These may be subdivided into intraepidermic and extraepidermic, and these, in turn, may be either "en masse" or "disseminated."

Basal cell epithelioma may occur anywhere on the skin and even on the mucous membrane. The growth is composed entirely of basal cells which have hyperchromatic nuclei and only a small amount of cytoplasm, and the cell outlines are not present. While normal basal cells contain prickles, those of the neoplasm do not. There may be some mitotic figures, but they are not abundant. The tumor may come from one point or many points (multicentric). This is of little import except in the case of superficial basal cell epitheliomatosis. It may take on any configuration, even simulating that of glandular tissue. Pigment and cystic formation may or may not be present.

Spinobasal cell epithelioma is synonymous with intermediary or transitional cell epithelioma. This type, in the main, is a basal cell epithelioma, within which there may be some whorls and pearls, and prickles are seen in some areas.

Epitheliomas developing in the sweat apparatus are of the basal cell variety. These may develop from the duct or from the glandular portion.

While it is generally agreed that the spinobasal cell epithelioma can and at times does metastasize, it is doubted by many that this can take place in a pure basal cell variety. However, I believe that even this type does metastasize, as I have specimens to show such occurrence.

This paper is the eighth in a "Symposium on Diagnosis and Treatment of Cutaneous Cancer," held at the New York Academy of Medicine, Section of Dermatology and Syphilis, on April 4, 1944.

The term "prickle cell epithelioma" is more scientific than "squamous cell epithelioma." As squamous cells cannot proliferate, naturally they cannot give rise to a neoplasm. However, the term has been used so long that it is still retained. The diagnosis of this variety depends not only on the hyperplasia of prickle cells but on the evidence of malignancy in them, such as whorls, pearls, keratinization, mitotic figures, anaplasia and dyskeratosis. Pearls, keratinization and accelerated dyskeratosis are present in the less malignant epithelioma, while whorls, mitotic figures and retarded dyskeratosis are to be seen in the more malignant epithelioma. In grading prickle cell epitheliomas one must consider not only Broder's classification but the aforementioned evidences of malignancy. For classification of a carcinoma grade 4, regional lymph nodes should be present.

In considering the malignancy of basal cell and prickle cell epitheliomas, one must pay special attention to the state of the palisade layer and also to the inflammatory protective zone. When the palisade layer is intact, the neoplasm is intraepidermic and therefore "en masse"; with a disruption of this layer the neoplasm is extraepidermic and either "en masse" or "disseminated." It is then clear that with an intact basal cell margin, regardless of the type, the tumor is relatively benign and there is no opportunity for metastasis.

The inflammatory zone beneath the growth is considered by some as one of the predisposing factors for the development of the tumor. Others, however, feel that it is a protective mechanism. I agree with the latter group and feel that a productive inflammatory zone is present in the less malignant neoplasms while the exudative protective inflammatory zone indicates a more malignant process. The inflammatory protective zone is an aid not only in diagnosis but in prognosis.

The last, and most malignant, group is that of the anaplastic, embryonic or undifferentiated cell epitheliomas. In general, the cells are large, with large deeply stained nuclei, a considerable amount of cytoplasm, which becomes somewhat granular, and distinct cellular outlines. The cells are usually round and have many mitotic figures. When the cells divide by amitosis, rather than mitosis, the malignancy is increased.

Of this group the least malignant is Bowen's tumor, a neoplasm which is rare. It develops from preexisting Bowen's disease. The cells are large but vary in size. They have many multinucleated cells (Bowen's cells), and frequently there is a clear cytoplasm. The prickles are lost.

The next group is that of the anaplastic epitheliomas which may arise directly from the epidermis or from the periphery of a previous basal cell or prickle cell epithelioma. When the tumor arises directly from the epidermis, it is frequently from a senile keratosis. Lesions

on the mucocutaneous junction often show evidences of malignancy without neoplastic development. These do go on to anaplastic epithelioma. Of course, one must be careful to rule out pseudoepitheliomatous changes.

Paget's tumor develops from either the epidermis or the ducts or both. Although many authors have reported extramammary primary Paget's disease, I do not believe that this occurs. There is considerable doubt whether the reported cases were not cases of Bowen's disease rather than of Paget's disease.

There are some terms that need a few words of explanation. I do not use the term "epidermoid carcinoma." A carcinoma may originate from the epidermis or follicle; some come from both. In general, those from the follicle wall are not so malignant as those from the epidermis. Instead of stating that a carcinoma (epithelioma) develops in situ, I use the terms "intraepidermic" or "extraepidermic." The term "spindle cell epithelioma" is a misnomer. In many instances in which the tumor is large or is growing into fibrotic tissue the cells will become compressed and flattened and appear spindle shaped.

The classification of epithelioma of the skin into basal cell, prickle cell and anaplastic cell is given in order of their degree of malignancy. While there may be considerable overlapping in specific instances, in general the classification is correct. The degree of malignancy varies from relative benignancy to highest malignancy. The epitheliomas of slightest malignancy are of such a nature as to make some authorities believe that they belong among the nevi rather than among the carcinomas.

Finally, in many cases the pathologic picture is necessary not only to make a diagnosis of epithelioma but to show the variety and activity of the lesion and, therefore, is most essential in the prognosis and successful treatment of the disease.

DISCUSSION

ON PAPERS OF DRS. TRAUB, ANDREWS, WEBSTER, PACK, HARRIS, LENZ, STOUT AND SACHS

DR. ANTHONY C. CIPOLLARO, New York: It has been a great privilege to listen to so many renowned experts in the field of cancer. Although it is difficult to discuss all these papers, I shall reiterate some of the more important points pertaining to the general subject of cutaneous cancer.

Drs. Stout and Sachs have described the essential features of the main varieties of cancer and in the main are in agreement on all important details. I think that in a discussion of cancer of any organ or of any type it is always important to emphasize the danger of metastasis. It is true that basal cell epitheliomas do not metastasize except in extremely rare instances, as Dr. Stout said, but squamous cell epitheliomas do metastasize, especially when they are either neglected or poorly treated. Bowen's disease has been considered to be a precancerous dermatosis, but, as Dr. Stout pointed out, it is a true intraepidermic epithelioma and occasionally it may take on characteristics of a squamous cell epithelioma.

Dr. Traub classified the clinical types of basal cell epitheliomas. This classification is important not only in visualizing the various clinical types but in evaluating their course. I am sorry that I have to disagree with a few minor details. Extensive lesions of basal cell epitheliomas on the eyelid, in my opinion, are better handled by a surgeon. No one can doubt the excellent results obtained by Dr. Traub in the treatment of this and other types of extensive basal cell epitheliomas, but I doubt that there are many dermatologists who are as skilled as he is in handling these cancers with electrosurgical eradication. Small lesions on the ear, even of the squamous cell variety, rarely if ever metastasize and are well handled by electrosurgical destruction. I have found that the multiple superficial type of basal cell epitheliomas is resistant to radiation, and my preferred method of treatment is with electrosurgical excision and curettage under procaine hydrochloride anesthesia.

Drs. Pack and Webster adequately emphasized the importance of selection of cases. Not all cutaneous cancers are amenable to the same type of treatment, even to the same type of surgical procedure. The many factors, such as age of patient, duration, location and size of lesion, type and grade of malignancy, previous treatment and type of soil from which the epithelioma arises, are important considerations in the selection of the proper method of treatment. Dr. Webster is right when he states that the healing period is long after electrosurgical procedures. I agree with him, but against these disadvantages there are certain advantages of electrosurgical procedures, some of which have already been mentioned by Dr. Traub. Some of the advantages are the elimination of hospitalization and general anesthesia and the minimizing of shock, nervous tension and expense. Most electrosurgical procedures can be carried out in an office with procaine anesthesia, just as any simple minor operation is.

Dr. Harris showed that many cutaneous cancers which can be adequately treated by surgical procedures also can be treated with irradiation. He also discussed in a limited way the mechanics and the physics of roentgen ray therapy. He is particularly partial to contact therapy for the treatment of superficial cancer. Since Dr. Harris brought up the question why dermatologists do not use contact therapy oftener, it may be well to mention a few reasons. Contact therapy is of limited usefulness in dermatology. It is useful only for small lesions, such as cutaneous cancers, warts, keratoses and other small similar lesions, because the field of irradiation is small. Most of the dermatoses that a dermatologist is called on to treat are generalized, and contact therapy apparatus would be inadequate for this purpose. Another reason why it is unnecessary for a dermatologist to have an extra expensive machine in the office is that practically everything that can be done with a contact therapy apparatus can also be done with a modern shock-proof machine. The only possible difference is that instead of delivering a cancer-killing dose in twenty to thirty seconds it may take a minute or two. In other words, the increased intensity obtainable with the contact apparatus can also be obtained with a modern shock-proof apparatus by decreasing the distance between the surface of the lesion and the anode.

I do not believe that dermatologists should minimize the danger of either an acute or a chronic radiodermatitis. One must bear in mind, as statistics show, that in about 25 per cent of the patients with radiodermatitis cancer develops. Many dermatologists over a period of years have experienced, and so have I, that following a single erythema dose of roentgen rays atrophy and telangiectasia developed years later. One should not forget the disastrous results from treating hypertrichosis with roentgen rays. One is justified in obtaining a first or second degree radiodermatitis during treatment of cutaneous cancer, but one is never

justified in obtaining roentgen erythema during treatment of inflammatory dermatoses. It is also my conviction that a simple basal cell epithelioma should not be treated with such intense radiation that radiation ulceration is produced, because a basal cell epithelioma is benign and nonmetastasizing whereas the epithelioma which follows a severe radiodermatitis or a radiodermatitic ulcer is of the squamous cell type and may be metastatic. I do not believe that dermatologists are justified in risking the development of a more serious type of cutaneous cancer in order to cure one of a benign type.

I was glad that Dr. Lenz showed what can happen when a cancer is poorly or inadequately treated. The surgeons as well as the radiologists have stressed the point that cancer must be destroyed completely when it is first seen. Temporizing with a little bit of desiccation or a little bit of roentgen rays or with solid carbon dioxide, with an acid or with the electrolysis needle not only is inadequate treatment but actually subjects the patient to greater danger than if the lesion had been left alone. When a combination method of treating a cutaneous cancer is used, each method must be of sufficient intensity if used alone to destroy a cancer. This brings up the question as to what advantage there is to a combination method. In most instances either surgical treatment which includes electrosurgical procedures or radiation alone is sufficient for practically all lesions. When the two methods are judiciously and expertly combined, the results from the treatment of all types of cutaneous cancers are almost perfect. In rare instances in which the tumors are deeply infiltrating or are inaccessible, a combination of radiation and surgical excision is of inestimable value. Those treating cancer realize that critical judgment based on experience is of the utmost importance in carrying out any treatment aimed at destroying cutaneous malignant neoplasms.

Two of the speakers mentioned the development of basal cell epitheliomas in radiodermatitis and in chemical burns. This must be considered most unusual, because the type of epithelioma which usually develops in radiodermatitis or in chemical burns is of the squamous cell variety. Of course, in radiodermatitis even sarcoma may develop, but this is also extremely rare.

The speakers did not advocate extensive, widespread and heroic surgical treatment for basal cell epitheliomas, nor were excessive doses of roentgen rays recommended for the treatment of these relatively benign cutaneous neoplasms. From their discussion I gathered that the average dose administered for an ordinary epithelioma without metastasis is in the neighborhood of 4,000 r. I am glad that doses of 20,000 or even 10,000 were not recommended. Such tremendous doses for the treatment of cutaneous cancer are never justified, in my opinion.

One further point to be emphasized is that a patient with a severe or dangerous cutaneous cancer is apt to do better when the method of treatment is selected by a cancer team, made up of a surgeon, a radiologist, a dermatologist and a pathologist. Some institutions already have such a setup. It is unfortunate that all those institutions treating cancer do not have such cooperative facilities. It is gratifying to note that mortality statistics of cutaneous cancer have shown an improvement while mortality statistics for cancer of other organs continue to rise.

In summarizing, I wish to emphasize particularly the following points: 1. I oppose the extreme measures employed by some in treating basal cell epitheliomas, because there is no necessity for them. 2. Each case of cancer of the skin presents a different problem and requires individualized rather than routine treatment. 3. Some cases of cutaneous cancer require the combined judgment of a cancer team for optimal results. 4. Inadequate treatment is to be condemned.

AN UNUSUAL CASE OF WARTS

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THE clinical report of this case seems justifiable for various reasons. Because of the lack of treatment, the warty lesions became extensive, numerous and abnormal in size.

On the dorsal surface of each foot there was a veritable warty carapace which covered the whole of the underlying skin surface. Both

Fig. 1.—Plantar warts in form of mosaic.

the finger nails and the toe nails were affected by the disease, the latter more than the former. The inner and outer canthi, which were affected, are not frequent sites for warts. On the palmar and plantar surfaces, besides the large number of warts there was hyperkeratosis. The hyperkeratosis of the palms was due to the patient's occupation—he was a

farm hand—while the plantar hyperkeratosis was due to a variety of traumatisms caused by the habit of going about barefoot.

Neither direct nor cultural mycologic examination showed the presence of fungi. Histopathologic examination showed extensive common

Fig. 2.—Common warts covering entire dorsa of the feet. Toe nails extensively involved.

palmar and plantar warty growths which were associated with hyperkeratosis.

REPORT OF CASE

A. D., a 30 year old unmarried Brazilian farm hand living at Curvelo, in the district of Santa Rita do Cedro, was admitted to Prof. Antonio Aleixo's ward on May 7, 1941.

Family History.—The parents and five brothers of the patient are alive and healthy. Two brothers had warts which disappeared spontaneously. Collateral relatives are in good health.

Personal History.—The patient had measles, whooping cough and chickenpox in infancy, but there was nothing else of interest in the history.

History of the Present Disease.—The patient stated that about fifteen years previously numerous lesions appeared on his forearms, hands, legs and feet; these lesions have persisted.

Fig. 3.—Common warts on the dorsa of the hands.

Fig. 4.—Common warts at the internal angle of the palpebral fissures.

Physical Examination.—General examination revealed nothing abnormal. The mucous membranes were healthy.

Dermatologic Examination.—The lesions were situated on the forearms, hands, legs, feet and inner and outer canthi of the eyes. All the primary lesions except those on the palmar and plantar surfaces were found to be proliferating monomorphous rounded papules with a grayish surface covered with small erect projecting corneal salients. The papules were firm to the touch and were movable over the underlying plane. They caused no neighboring inflammation and were quite painless. The palmar and plantar lesions were different, because some of them were smooth localized hyperkeratoses while others were hyperkeratoses with

Fig. 5.—Section showing histologic structure of common warts. Lesion on the right palm.

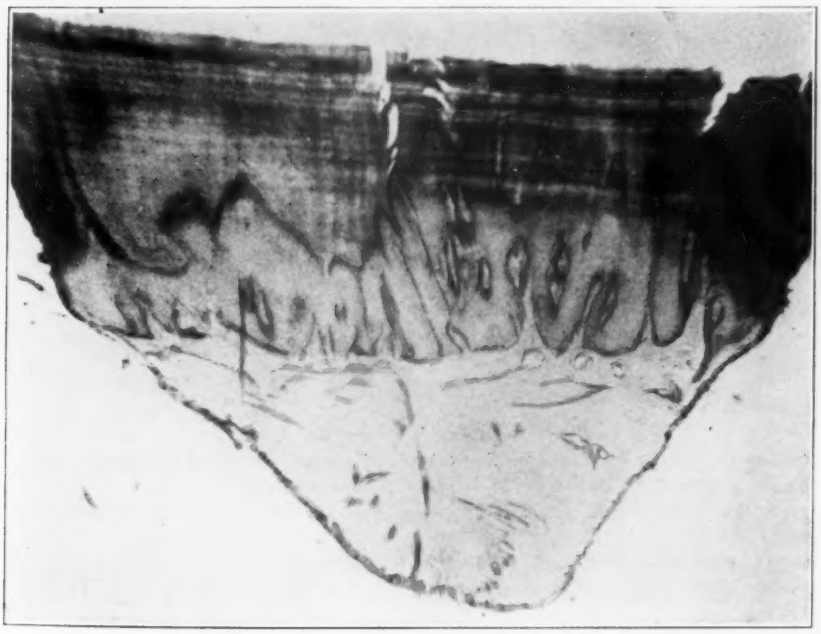

Fig. 6.—Section showing histologic structure. Lesion on the left sole.

grooves and hollows. The palmar and plantar lesions were painless, for the patient did all kinds of manual labor and walked barefoot. On each sole there was diffuse hyperkeratosis which at some points showed intersecting furrows and well marked hollows (fig. 1). But when the lesions as a whole were analyzed it was seen that they were confluent, completely covering the underlying skin with a veritable warty carapace. Some toe nails were dystrophic, loose from their nail beds and wholly or almost entirely covered with warts (fig. 2). Nearly all the nail beds were affected. Grayish slightly raised lesions were seen on the legs,

Fig. 7.—Section showing histologic structure. Lesion on the dorsum of the left foot.

and there were two gigantic warts on the left knee. There were numerous warts on the backs of the hands, some of them isolated and others confluent, as on the right forefinger, which was completely covered. There were periungual and subungual lesions (fig. 3). On both palms the warts were numerous and disseminated, some being smooth and others rough or furrowed. There were two warts at the inner canthus of each eye (fig. 4).

Laboratory Examination.—The Wassermann and Kahn reactions were negative. Direct and cultural examination did not reveal fungi. The histopathologic exami-

nation was carried out by Dr. Junqueira, whose report was as follows: "In all the specimens the lesions observed were the same—hyperkeratosis, hypergranulosis, hyperacanthosis and papillomatosis. There was slight perivascular infiltration of lymphocytes. In two of the sections, 1 and 3, the rete plugs were longer and flattened (figs. 5, 6 and 7).

The anatomopathologic diagnosis was: common warts of the palmar and plantar variety.

Rua Ceará, 1691.

EPIDERMOLYSIS BULLOSA SIMPLEX OF THE HANDS AND THE FEET

A Genetic Study of the Hereditary Type

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EPIDERMOLYSIS bullosa is a disease of the skin which is captious in its various manifestations. Of these, involvement of just the hands and the feet without any residual scarring or other cutaneous changes is one of the most unusual.

In 1895 Elliot [1] reported the first of such cases, that of a 30 year old white man who had suffered from the disease since he was 5 years of age. The bullae manifested themselves especially in warm weather. The bullous elevations arose without precedent redness after walking or rowing or after using a hammer or screwdriver. There was an associated hyperhidrosis of the hands and the feet and often bromhidrosis of the latter. There were no subjective symptoms except pain after the bullae had ruptured and left raw surfaces. Examination revealed bullae of all sizes on the hands and the feet, some of which had arisen on the latter during his walk to the consultation. Treatment of many types had been tried but was of no avail. The patient's father had bullae only on the feet.

Lustgarten [2] a year later stated that he had 2 patients who had blisters involving only the palms and the soles. He expressed the belief that these milder types of epidermolysis bullosa were not so rare.

Records of all persons described in this report are on permanent file in the Heredity Clinic, University of Michigan.

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* Studies and contributions from the Department of Dermatology and Syphilology of the University of Michigan Medical School; service of Dr. Udo J. Wile and Dr. Arthur C. Curtis.

† Studies and contributions from the Department of Human Heredity of the Laboratory of Vertebrate Biology, University of Michigan.

1. Elliot, G. T.: Two Cases of Epidermolysis Bullosa, J. Cutan. & Genito-Urin. Dis. **13**:10-18 (Jan.) 1895.

2. Lustgarten, S., in discussion on Elliot, G. T.: A Case of Epidermoloysis Bullosa, J. Cutan. & Gen.-Urin. Dis. **14**:26-27 (Jan.) 1896.

This view was also expressed by Waisman.[3] Greenberg[4] found an incidence of 0.2 per cent among dermatologic patients seen in an army station hospital during a two year period. More recently, Mooney[5] has reported an incidence of 0.4 per cent.

Since the original cases of Elliot[1] and Lustgarten,[2] others have been presented by Cane,[6] Gilmour,[7] Cole and Driver,[8] Wertheimer[9] and Lerner.[10] Cockayne,[11] in his interesting article entitled "Recurrent Bullous Eruptions of the Feet," cited an instance in which a brother of one of his patients had blisters on the hands as well as on the feet. Since 1942 reports calling attention to the importance of recognition of the mild form of epidermolysis bullosa in members of the armed forces have been noted by Leider and Baer,[12] Mansur,[13] Frank,[14] Waisman,[3] Greenberg[4] and Mooney.[5] In some instances, a medical discharge from the service had been necessary owing to the impossibility of preventing or controlling blistering of the hands and the feet. The failure to differentiate the cause of the bullous formation from dermatophytosis, dermatitis venenata and impetigo of the feet had necessitated much useless hospital care, prior to the recognition of the disease by the aforementioned observers. During a period of rest in bed, the lesions of the hands and the feet responded well to any form of therapy. In a few instances blisters immediately appeared after resumption of walking even about the ward. These authors recognized and stressed

3. Waisman, M.: Recurrent Bullous Eruption of the Feet and Hands, J. A. M. A. **124**:1247-1250 (April 29) 1944.

4. Greenberg, S. I.: Epidermolysis Bullosa, Arch. Dermat. & Syph. **49**: 333-334 (May) 1944.

5. Mooney, J. L.: Epidermolysis Bullosa, Arch. Dermat. & Syph. **50**:167-169 (Sept.) 1944.

6. Cane, L. B.: Epidermolysis Bullosa, Brit. M. J. **1**:1114-1116 (May 8) 1909.

7. Gilmour: Epidermolysis Bullosa, Arch. Dermat. & Syph. **4**:267 (Aug.) 1921.

8. Cole, H. N., and Driver, J. R.: Epidermolysis Bullosa Hereditaria, Arch. Dermat. & Syph. **18**:941 (Dec.) 1928.

9. Wertheimer: Epidermolysis Bullosa Hereditaria, Arch. Dermat. & Syph. **21**:706 (April) 1930.

10. Lerner, C.: A Case of Epidermolysis Bullosa, Arch. Dermat. & Syph. **23**: 772 (April) 1931.

11. Cockayne, E. A.: Recurrent Bullous Eruption of the Feet, Brit. J. Dermat. **50**:358-362 (July) 1938.

12. Leider, M., and Baer, R. L.: Epidermolysis Bullosa Hereditaria, Arch. Dermat. & Syph. **46**:419-424 (Sept.) 1942.

13. Mansur, H. D., Jr.: Hereditary Epidermolysis Bullosa, J. A. M. A. **120**: 1122-1124 (Dec. 5) 1942.

14. Frank, S. B.: An Unusual Variant of Epidermolysis Bullosa, Arch. Dermat. & Syph. **47**:327-334 (March) 1943.

the familial features of the bullous disease of the hands and feet. The mode of transmission of the disease was called a dominant, a dominant possibly through a single pair of genes, and a conditional dominant, since it was not known in the homozygous state. Apparently all described simple epidermolysis bullosa transmitted through a dominant gene, since each person cited with bullae had a parent with bullae and since the ratio of affected to nonaffected offspring of a defective parent approached 1 : 1 when the parents were a heterozygote and homozygote normal. That this dominant is different from the one causing the dystrophic type of epidermolysis bullosa is evidenced by the fact that in no kindred in cases in which the simple form is present does one find the dystrophic form, which is characterized by epidermal changes such as scarring, milia and acrocyanosis. The manner in which the aforementioned kindreds exhibit bullae in the same location, namely

Fig. 1.—Character of bullous lesions on foot of VI A 14-3, a first cousin of propositus.

the hands and the feet, would indicate that one has a genetic entity in the simple type which is as unique in its picture as that, described by Cockayne [11] and others, in which bullae were found only on the feet.

The following report presents another case of epidermolysis bullosa of the simple type involving the hands and the feet, in which a study of the family pedigree uncovered a hitherto unrecognized relationship between the families cited separately by Mansur [13] and by Cartledge and Myers.[15]

REPORT OF A CASE

S. D. (VI A 15-3), a white man of Irish-British-Dutch extraction, aged 27, was seen in the outpatient service of the University Hospital on June 11, 1942.

15. Cartledge, J. L., and Myers, V. W.: Inherited Foot-Blistering in an American Family, J. Hered. **34**:24 (Jan.) 1943.

He complained of blisters on the hands and feet. This eruption had been reappearing since infancy, particularly during the hot summer weather. Blisters would occur in the winter after he had played basketball or football for a very few minutes. Many times when there were blisters on the feet there were none on the hands. The chopping of wood or the pumping of gasoline in a service station would cause blisters in a short time. In an area where a blister was going to develop, the patient would sometimes notice a slight burning. There were no sensations after the blisters formed unless the surface was denuded, in which case there was a feeling of soreness and burning. Rupturing a bulla would cause healing in five to seven days, rather than ten to fourteen. Infection or scarring had never occurred. Bullae had never been present elsewhere on the body. The patient felt socially inadequate because of the family stigma under which he suffered.

Gross Examination.—On the mediodorsal and palmar surfaces of the second and third fingers of each hand as well as on the palm were six to ten tense bullae. There were three bullae on the plantar surface of each foot. The skin surrounding the newer bullae was clear, whereas the skin about the older bullae was erythematous. The roof of each bulla was tense and thin. The newer lesions contained straw-colored fluid, whereas the older ones were filled with a turbid milky material. There were hyperhidrosis and bromhidrosis. There was no scarring, milia, pigmentation or acrocyanosis. The teeth, hair and nails showed no abnormal changes. Nikolsky's sign was not elicited. The results of the physical examination were essentially normal.

Laboratory Examination.—Examination on several occasions showed the urine to be normal. The hemoglobin content was 85 per cent, and the white blood cell count was 5,400. The Kahn reaction for syphilis was negative. Scrapings of the skin from the interdigital spaces of the feet revealed no fungi, either on microscopic examination of a 15 per cent potassium hydroxide preparation or by growth on Sabouraud's culture medium. Results of similar examinations for the presence of fungi in members of the patient's immediate family (VI A 15-2, -3, -5, -7 and V A 8-1) were negative.

FAMILY HISTORY

Many members of the patient's family (fig. 2) had suffered from recurrent bullous eruptions limited to the hands and the feet. This disease could be traced back to a forefather who had come from Ireland about 1770 to settle in what is now West Virginia. The tendency toward and the ease of blistering varied in a sibship rather than between sibships. In most members of the family, blistering was slight. This was particularly true as the person became older. Some of the members of the family had been in the armed forces and had been hospitalized for dermatophytosis. Rapid response to rest in bed with immediate recurrence on resumption of marching had resulted in medical discharges from the army without the cause of the bullous condition being recognized. Some members of the family found difficulty in doing manual labor during the summer because of the decided tendency for blisters to develop. Members of the family knew that walking on the hot cement sidewalks for ½ to 1 mile (800 to 1,600 meters)

would cause blisters of the feet. Walking the same distance on the grass or in the dusty street would be less apt to cause trouble. Ironing would cause blisters on the hands of many of the housewives. Scarring had never taken place in any of the persons who had suffered from bullous eruptions.

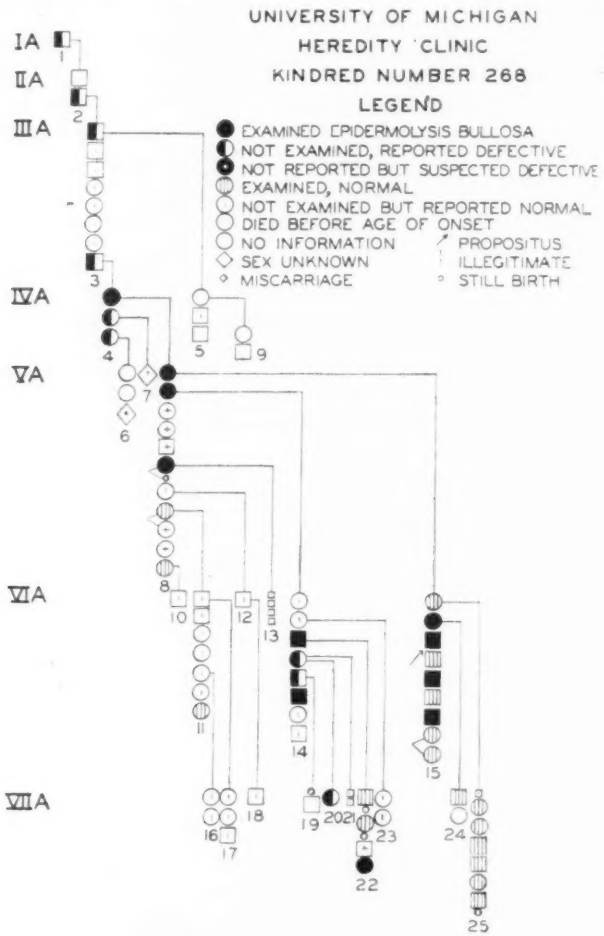

Fig. 2.—Family tree of family *A*.

These family trees (figs. 2 and 3) have been drawn in a style devised by Dr. C. W. Cotterman. The sibships are shown in a vertical sequence, with the oldest member within a sibship at the top as number 1, progressing with the order of birth date in series as one passes downward. An occasional symbol stands for more than one person, the number of persons then being indicated by an Arabic numeral enclosed within the symbol. References will be made to individuals by combining generation numeral and letter *A* or *B* for one of the two families, with the sibship number, a dash and then the individual number within the sibship, as IV A 4-3 for the third child in family *A*, generation *IV*, sibship 4.

Of this family of 105 persons (family A), consisting of seven generations, 10 males and 10 females had suffered from the disease. Whether or not the disease was present in 39 members was unknown; the chances are that none of these 39 who reached adulthood were affected, since we noted that almost everybody was aware of the condition of the persons who had bullae but not of those who did not have bullae. The children of defective parents include 19 affected, 22 normal and

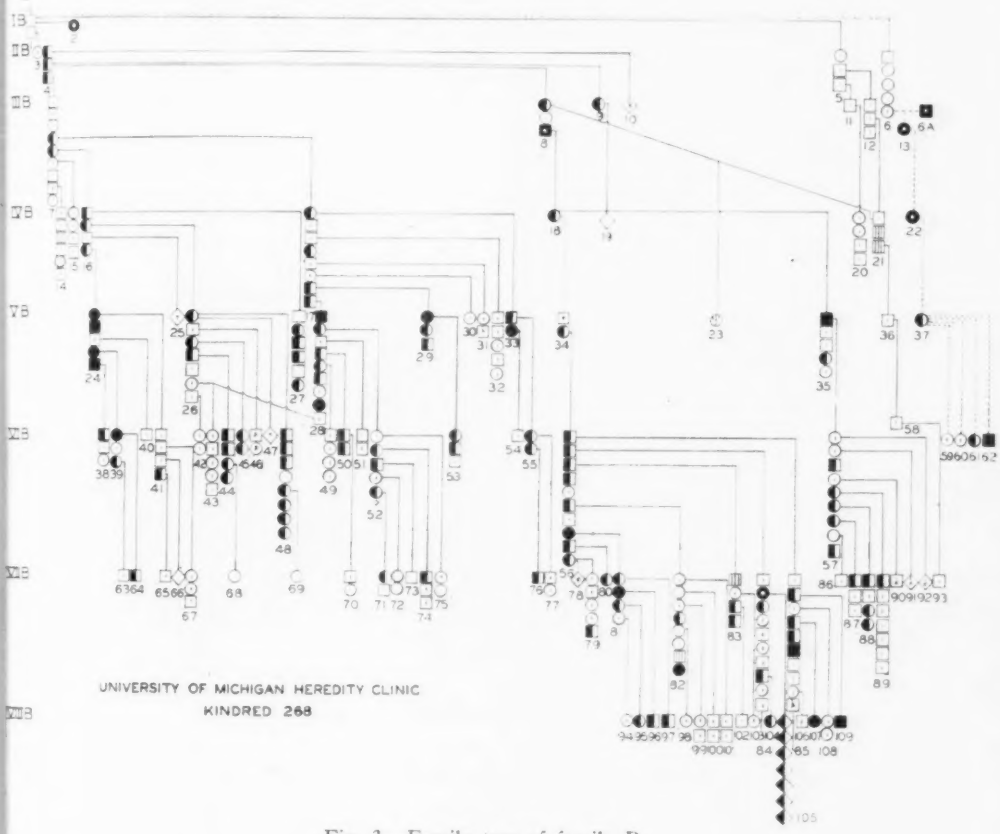

Fig. 3.—Family tree of family B.

39 of questionable status. In every instance in which there was an affected child, a parent was affected. There was no history of consanguinity.

COMMENT

Recurrent bullous eruptions of the hands and the feet were referred to as Weber-Cockayne's localized epidermolysis bullosa by Waisman,[3] who stated that Weber described the first case in 1926. It would seem

that credit should be given to Elliot,[1] who in 1895 first reported completely the case of a patient in whom there were bullae only of the hands and feet. Weber's and Cockayne's patients, except in a single instance, had bullae of the feet and not of the hands and the feet.

The variation in severity and the presence of bullae in hot weather have been stressed by Waisman [3] and others. This is apparent in our series. The decided tendency of the bullae to be worse in summer weather and hot weather has caused a recent interest in pathologic porphyrin metabolism and epidermolysis bullosa. Unfortunately, we were unable to study this interesting problem in any of our cases.

A congenital deficiency of elastic tissue has been considered to be the underlying cause of the bullae by some. A biopsy of a member of our group which we studied showed no abnormality of the elastic tissue. This observation has been made by others in the simple form of epidermolysis bullosa. The superficial location of the bullae, between the

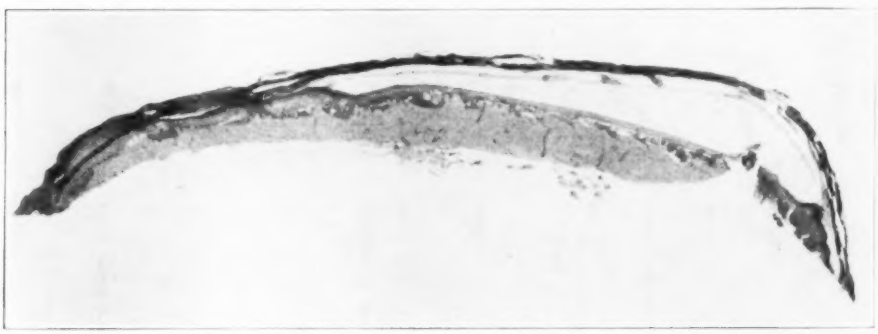

Fig. 4.—Section from the sole of a 9 month old girl (VII A 22-6) showing hyperkeratosis and parakeratosis. The stratum corneum forms the top of a large bulla which is monolocular and which contains no cells. The stratum granulosum is thickened. There is irregular acanthosis with spongiosis. There is dilatation of the capillaries in the upper part of the cutis. There is perivascular infiltrate of round cells. Weigert's elastic tissue stain of the same tissue reveals no change in the distribution or number of elastic tissue fibers.

stratum corneum and the stratum granulosum, no doubt accounts for the lack of scarring in any of this series.

The tendency of the epidermis to react to local friction, pressure, heat and moisture with bullae—and not with thickening and scarring—is a notable feature. Waisman [3] described this as a passive yielding to the presence of fluid exuded beneath the epidermis to physical irritation. Lustgarten [2] suggested that it was related to factitious urticaria, while Unna, cited by Elliot,[1] said that it was a dermatitis, traumatic in nature, a concept which Elliot also held. On the other hand, Mansur [13] expressed the belief that when the Schneider index was + 11, cutaneous or vascular irritability as an etiologic factor was ruled out.

Whatever the cause of the bullous lesions may be, their varying location on different subjects is indicative of differing genetic entities. It is characteristic of the entire kindred in which a form of epidermolysis bullosa hereditaria occurs that they exhibit bullae in the same location. In other words, bullae may occur only on the palmar and plantar surfaces, in which case they will be found on these surfaces alone throughout the kindred. Or bullae may be found only on the feet, face, elbows or mucosal surfaces.

It was while we were getting data on the persons in family A who resided in Michigan, West Virginia and southwestern Pennsylvania, that we discovered the heretofore unrecognized relationship between the families reported by Cartledge and Myers [15] and by Mansur.[13] At first there was considerable confusion as to whether or not all those in family A and family B were of the same family pedigree. We found ourselves frequently looking up sibships in the family under chart A which belonged to family B. Many in family A or B named as relatives persons whose names appeared on the other chart. The original propositus (VI A 15-3) told us of "some sort of cousins," naming VI B 56-8 and V B 35-5, who blistered. There are certain facts which make relationship between persons in families A and B a probability. The nature of the disease is unusual, and to have two large families bearing the same trait, as shown in figures 2 and 3, living in the same small locality for over two hundred years without there being a common forebear would be most unusual. Furthermore, the surnames of the persons suspected of introducing the defect into the two families I A 1 and I B 2 and the spouse of (III B 6-5) were the same. The frequency of certain unusual given names was striking and suggestive of relationship. The first person reported to show the defect by Cartledge and Myers [15] was a man (II B 4-3) whom they believed to be an offspring of the second marriage of the father (I B 1-1), who came to this country in the last third of the eighteenth century. However, we have conclusively found that II B 4-3 was in fact a son of the first marriage and that only the offspring and descendants of this marriage were affected, which would indicate that the blistering was not brought into the family by the male ancestry. In addition, it was found that illegitimate children (II B 6) of the father (I B 1-1) were not bothered with the bullous disease. His first wife (I B 2) was therefore suspected of blistering since all of her children, and only her children, blistered, as did many of her descendants. Considering this and their surnames, it would seem likely that the family (I B 2) was related by blood to the second family (I A 1). Mansur started his pedigree with a great grandmother (IV B 18), whom we found to be a great granddaughter of the man designated as (I B 1-1). It was through

this family tieup that we were able to connect the pedigrees of Cartledge and Myers [15] to that of Mansur.[13]

Family B represents 356 persons. Some of the sibships have been reported in material which has been published previously. Cartledge and Myers [15] reported the following sibships: 16, 24, 26, 27, 28, 31, 34, 38, 39, 40, 41, 42, 43, 44, 50, 51, 54, 63, 64, 65, 66, 67, and 73. They showed the following sibships incompletely, or with discrepancy from ours: 1, 2, 4, 5, 6, 7, 17, 30, 49, 70, 71, 72, 74, and 75. In Mansur's paper the following sibships have been completely shown: 56, 83, 84, 85, 95, 97, 100, 101, 102, 106, 107, 108, and 109. The following sibships were incompletely shown, or show some discrepancy from ours: 18, 79, 80, and 81. This study yields the following fifty-four additional sibships: 3, 8, 9, 10, 11, 12, 13, 14, 15, 19, 20, 21, 22, 23, 25, 29, 32, 33, 36, 37, 45, 46, 47, 48, 53, 55, 57, 58, 59, 60, 61, 62, 68, 69, 76, 77, 78, 82, 86, 87, 88, 89, 90, 91, 92, 93, 94, 96, 98, 99, 103, 104, 105, and 106.

There are 56 affected men and 62 affected women with the sex of 7 of the affected persons not known. The condition could not be determined in 35 offspring of affected parents. The children of defective parents include 123 affected, 93 normal and 35 questionably affected.

Combining families A and B, we find that in 461 persons there were 66 males and 72 females affected. Of 7 affected persons the sex was unknown. The children of defective parents include 142 affected, 115 normal and 74 of questionable status.

When the material in figures 2 and 3 is tested by the chi-square method for statistical deviation from the normal in the sex ratio of the affected persons, the raw material being taken from all the sibships which could be considered susceptible to the trait (i. e., all sibships having one affected parent), chi-square is 0.260—an insignificant deviation. This rules out sex linkage or limitation. When this material is tested for statistical deviation from the normal in ratio of affected to normal persons, the raw material for the test being taken only from susceptible sibships in which the condition of all the sibs was known to us (eliminating any sibships in which there were early deaths, premature births, stillbirths or persons of unknown condition), chi-square equals 0.268—again an insignificant deviation.

Since Greenberg [4] found that all his patients inherited the condition from the mother, we have tested our material from figures 2 and 3 by the chi-square method to see whether there is any evidence of either sex being the commoner transmitter. We found that the defect was transmitted by 30 mothers and 23 fathers, with a chi-square of 0.924, which shows an insignificant deviation from the expected 1 : 1 ratio.

In our experience men did not have bullae as frequently as women, the ratio being 1.0 to 1.09.

Epidermolysis bullosa of all types seems to be a much more frequent disease than is commonly believed. However, papers and society transactions dealing with the simple type limited to the hands and the feet have not been numerous, there being only 14 in the 213 that we reviewed. In no instance could we find as large a pedigree as we have presented in figure 3, in which there are data for 356 persons and of whom 125 are affected. Cartledge and Myers [15] reported 40 affected persons and Mansur [13] 30.

SUMMARY

The literature concerning epidermolysis bullosa hereditaria involving only the hands and the feet without scarring and other cutaneous changes is reviewed.

A case of epidermolysis bullosa with a family pedigree of 105 persons, of whom 10 men and 10 women suffered from the bullae of the hands and the feet, is reported (fig. 2).

The pedigrees of Mansur [13] and of Cartledge and Myers [15] are linked together, and 54 sibships are added, making a total of 109 sibships covering 356 persons, in which there are 56 affected men and 62 affected women, with the sex of 7 persons not being known. The probability of connection between families A and B is shown.

The genetic distinctiveness of different types of epidermolysis bullosa hereditaria as characterized by location of bullae on the body is pointed out.

A statistical study shows that neither the ratio of normal to affected progeny of an affected parent nor the sex ratio of affected offspring nor the ratio of male to female parent is of significant deviation from the expected 1 : 1, proving that we are dealing with a simple mendelian dominant trait.

A plea against the use in the title of the names of either Weber or Cockayne for a disease which neither described is made. If a proper name is to be used in describing epidermolysis bullosa hereditaria of the simple type carried by a dominant gene limited to the hands and the feet, we suggest that of Elliot's.

A new method of plotting family pedigrees is used.

INTRAHEPATIC OBSTRUCTIVE JAUNDICE DUE TO NEOARSPHENAMINE

Ineffectiveness of Therapy

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RECENTLY Freis and Mater [1] reported a case of jaundice due to intrahepatic obstruction consequent to the use of oxophenarsine hydrochloride. Some years previously Hanger and Gutman [2] collected a series of 12 cases of such a disease following the use of arsphenamine. They described the clinical and pathologic aspects of these cases and contrasted the observations with those of cases in which the jaundice resulted from parenchymatous hepatic damage. The following case is believed to belong in the first of these two groups. The disease followed the use of neoarsphenamine. The case is of interest because of the lengthy duration of the jaundice, the fact that operation was not requested, and the ultimate rapid improvement with no treatment after the failure of prolonged and varied therapy in the hospital.

REPORT OF A CASE

A healthy 26 year old Negro, a stevedore, applied for antisyphilitic treatment in April 1944. He stated that two or three months previously he had received five intravenous injections of a yellow material from a physician in his neighborhood. There was no history of a primary or secondary syphilis, and his past history showed no serious illnesses, except an appendectomy with drainage in 1932 and gonorrhea at the age of 16. Physical examination in April 1944 revealed entirely normal conditions. The patient was well developed and well muscled and weighed approximately 170 pounds (77.1 Kg.). The Wassermann and Kline reactions were strongly positive. A provisional diagnosis of latent syphilis, probably late, was made. Treatment was begun with weekly injections of 0.2 Gm. of bismuth subsalicylate in oil for six weeks. Neoarsphenamine was then given, the first dose being 0.45 Gm. and the next two 0.6 Gm. each. There was no reaction to the first or second injection of neoarsphenamine.

From the Medical Service A, Lankenau Hospital.

1. Freis, E. D., and Mater, D. A.: Intrahepatic Obstructive Jaundice Following Mapharsen, with Development of a Spruelike Syndrome, J. A. M. A. **126**:892 (Dec. 2) 1944.

2. Hanger, F. M., and Gutman, A. B.: Postarsphenamine Jaundice Apparently Due to Obstruction of Intrahepatic Biliary Tract, J. A. M. A. **115**:265 (July 27) 1940.

A few hours following the third injection, on June 2, the patient became nauseated, vomited repeatedly, felt weak and had a severe frontal headache. He also noted epigastric pain radiating upward along the sternum. Itching of ears and feet and dark red-brown color of his urine were observed shortly after the onset, and for several days he was unable to retain food taken by mouth. Accordingly, he was admitted to the hospital from June 7 to June 11, during which time he improved rapidly with symptomatic treatment and intravenous injection of 5 per cent dextrose in distilled water. Scleral jaundice was noted June 9, on which day there was also bile in the urine for the first time. The liver was not palpable at any time. The conditions observed on physical examination were otherwise unchanged. Laboratory studies showed: hemoglobin content, 88 per cent; red blood cells, 4,240,000 and white blood cells, 10,900, of which 72 per cent were neutrophils and 28 per cent lymphocytes. The urine was entirely normal on June 7. A faint trace of albumin appeared on June 8 and June 9. Bile was found on June 9. All microscopic observations were normal. The icteric index on June 9 was 26, and the prothrombin time was 100 per cent. During this period temperature, pulse and respirations were normal.

The patient was observed on an ambulatory status during the remainder of June and part of July. He felt well during this time, but the urine continued dark and the stools were light brown. Scleral jaundice was apparent, however, and on July 12 the icteric index was 100. The patient was again hospitalized, from July 12 through July 31. Questioning revealed intolerance to eggs, pork and cabbage since his previous admission and some generalized itching. Physical examination again gave no remarkable results, except pronounced scleral jaundice. The liver was still not palpable. Laboratory studies showed no change in the blood count. The urine continued to show bile and a trace of albumin, and granular casts were reported. The urea nitrogen level of the blood was 8 mg., the cholesterol level 227 mg., the serum proteins 7.81 Gm. per hundred cubic centimeters, and the prothrombin time was 100 per cent on two occasions. The icteric index rose gradually to 120. The cephalin flocculation reaction was 2 plus and the galactose tolerance test showed a total excretion of 0.9 Gm. in five hours. The sulfobromophthalein sodium excretion test was unsatisfactory because of the jaundice. Roentgenograms showed a normal chest and, after ingestion of barium sulfate, a normal stomach and duodenum. Biliary drainage was unsatisfactory.

There was no change in the condition of the patient in spite of daily intravenous infusions of 10 per cent dextrose in distilled water and a diet high in carbohydrates and protein and low in fat.

From July 31 through Sept. 7, 1944, the patient was followed in the outpatient department. During this time he had increased generalized itching, especially of the face and feet. In addition he continued to lose weight gradually until he was down to 145 pounds (65.8 Kg.), and a persistent annoying diarrhea developed, with four to six movements a day. The diarrhea was not relieved by the usual remedies. According to the patient the stools contained pigment, and his urine continued dark. At times he felt a little dizzy, and he constantly had a bitter taste in his mouth. By August 25 the icteric index was 200, and on September 8 the patient was again hospitalized. The principal abnormality at this time was the profound jaundice visible in the scleras and the soft palate. On September 16 the liver was palpable on deep inspiration. The edge was sharp and definitely tender.

Results of laboratory studies during this admission (September 8 to November 11) were as follows: The urine continued to show no urobilinogen, but it gave a strongly positive reaction for bile constantly and showed a faint trace of albumin

on repeated examinations. The hemoglobin was constant at 88 per cent, the red blood cells varied from 4,200,000 minimum to 4,880,000 maximum, and the white blood cells ranged from 6,100 to 10,700, with normal differential counts. The icteric index fluctuated considerably, but there was no positive trend, as shown by these values: September 12, 152; September 20, 180; October 11, 150; October 17, 135; October 31, 165; November 7, 225, and November 9, 180. The van den Bergh test elicited an immediate direct positive reaction on three occasions, with quantitative values for bilirubin in the serum of 13, 14 and 18 mg. per hundred cubic centimeters. The prothrombin time had fallen to 70 per cent since the last admission, but the use of vitamin K parenterally restored the figure to 100 per cent, where it remained throughout the patient's stay, even after the use of vitamin K was stopped. Serum proteins remained normal. On September 21 they were 7.6 Gm. per hundred cubic centimeters, of which 5.2 Gm. was albumin and 2.4 Gm. were globulin. Another determination on September 26 showed values of 6.86 Gm., 3.88 Gm. and 2.88 Gm. per hundred cubic centimeters respectively. The cholesterol level of the blood on September 13 was 216 mg. and on November 10, 298 mg. Fractionation, however, showed that only 30 per cent of the cholesterol was in the ester form. On September 26 the alkaline phosphatase activity was 8.5 units, and the serum amylase 16 units.

Results of tests of hepatic function on this admission were as follows. The cephalin flocculation reaction on September 20 was 2 plus; October 18, negative and on November 10, negative. The hippuric acid synthesis test on September 16 showed 0.9 Gm. excreted; on October 19, 0.9 Gm., and on November 9, 1.4 Gm. The galactose tolerance test showed 0.84 Gm. excreted on September 20, and none excreted on October 17. The sulfobromophthalein sodium excretion test was again unsatisfactory because of jaundice.

Other studies showed a normal gastric acidity, failure of biliary drainage to show B bile although bile salts were reported and a flat glucose tolerance curve, with values of 81, 104, 83, 69 and 64 at 0, one-half, one, two and three hours. A roentgenologic study of the gallbladder showed failure to concentrate any of the dye given by mouth. A barium sulfate meal followed by serial roentgenologic examinations showed slow progress through the jejunum with poor peristaltic function, some distention of the loops of the intestine and increased prominence of the mucosal folds. There was no evidence of obstruction however.

Therapy used during this final period of hospitalization was directed toward protection of the liver and attempts to promote the flow of bile. Daily intravenous infusions of 1,000 cc. of 10 per cent dextrose in water were given. Sorparin tablets (McNeill) (stated by the manufacturer to contain 3 grains [0.19 Gm.] of extract of Sorbus aucuparia [mountain ash]) were given, 3 after each meal, from September 24 through October 18. Beginning October 11 sodium dehydrocholate was added to the daily infusion, 10 cc. of 20 per cent solution being used. On the same day the patient received intravenously 10 Gm. of methionine in the infusion.[3] On each day subsequently 3 Gm. of methionine in water was given twice a day by mouth. This therapy was continued until the final discharge, on Nov. 11, 1944. Throughout the patient's stay a diet high in carbohydrates and protein was given.

Results of Therapy.—So far as could be observed none of the therapy described produced any definite improvement. The patient gained no weight. The icteric index showed no improvement; neither did the test of the hepatic function which was impaired (hippuric acid synthesis). There was symptomatic improvement of the itching and diarrhea. These were somewhat alleviated after admission and

gradually disappeared. The sodium dehydrocholate and methionine used did not cause any untoward effects, except for a single instance of nausea three days after their use was begun.

Following the patient's discharge on Nov. 11, 1944, there was immediate improvement, which continued steadily. He gained weight at the rate of 2 pounds (1 Kg.) a week, until the total gain was 30 pounds (13.6 Kg.) by February 1945. The icteric index fell each week, as shown by these values: November 9, 180; November 20, 120; November 28, 80; December 4, 70; December 11, 55; December 18, 45; December 26, 25; January 15, 1945, 15; May 7, 10. The patient felt well and soon returned to work. A final check of hepatic function was made at the end of January 1945, with these results: The cephalin flocculation reaction was negative; the hippuric acid synthesis test showed 3.9 Gm. excreted, and the galactose tolerance test, none excreted. The sulfobromophthalein sodium excretion test showed a very faint trace of the dye at ten minutes and none at twenty minutes; the prothrombin time was 100 per cent.

COMMENT

The facts observed in this case agree largely with the observations of Hanger and Gutman in their cases of intrahepatic obstruction. The onset occurred after the third dose in a series and showed an acute constitutional reaction with gastrointestinal symptoms predominating. There was prolonged painless jaundice with severe pruritus and loss of weight. For a prolonged period the bile was diminished in the stools and increased in the urine. The cephalin flocculation reaction was not greatly altered from the normal negative, and the tolerance for galactose was not impaired. The cholesterol level of the blood was definitely increased, and the ester fraction was lowered. The urea nitrogen of the blood remained normal.

However, the alkaline phosphatase value was not elevated; there was no apparent change in the serum protein or albumin-globulin ratio, and the hippuric acid synthesis was impaired on three determinations. These observations are in disagreement with those of Hanger and Gutman.

The use of methionine in this case was based on reports of Peters and his associates [3] and Beattie and Marshall.[4] These men reported that the use of methionine prevented or minimized damage to the liver during arsenical therapy and shortened the clinical course in cases of jaundice. Peters and his associates summarized their results and concluded ". . . that both cysteine and methionine had a significant but not remarkable effect on the course of the jaundice."

The failure of methionine and other forms of therapy to change the clinical course in the case reported here probably results from the basic

3. Peters, R. A., and others: Sulphur-Containing Amino-Acids and Jaundice, Nature, London **153**:773 (June 24) 1944.

4. Beattie, J., and Marshall, J.: Methionine in the Treatment of Liver Damage, Nature, London **153**:525 (April 29) 1944.

pathologic condition present, i. e., the blockage of the tiny bile canaliculi rather than actual damage to the parenchyma of the liver itself. The conclusion drawn is that this disease described by Hanger and Gutman runs a prolonged self-limited course, unaffected by the therapeutic measures used, and that time is the essential requisite for restoration to normal. Granted that the therapy may have been helpful in preserving the patient throughout his illness, there was no evidence of any specific action on the underlying pathologic changes.

SUMMARY

A case of prolonged, profound jaundice following the use of neoarsphenamine has been presented. The clinical and laboratory observations were those described in cases of jaundice due to obstruction of the bile canaliculi. Prolonged intensive therapy, including the use of methionine, produced no demonstrable improvement. The patient ultimately made a spontaneous complete recovery, following cessation of all therapy.

TREATMENT OF CONGENITAL AND OF ACQUIRED SYPHILIS IN INFANTS AND IN CHILDREN BY PENICILLIN

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FOR the past two years syphilis in adults has been treated with penicillin, and at the present time it is thought that this form of therapy has been encouragingly successful. Sixteen months ago, several of us became interested in the possibility of treating babies and children with congenital and with acquired syphilis with penicillin. As penicillin is less toxic than arsenicals and heavy metals, it was felt that an effort should be made to determine whether its therapeutic efficiency was comparable to that of arsenicals and heavy metals.

In the past sixteen months, we have treated 39 syphilitic children with penicillin. Eleven of these had acquired syphilis, and 28 had congenital syphilis. There has been 1 death in our series and 3 mild reactions. We do not as yet have any idea of the optimal dosage of penicillin in the treatment of syphilis. We have used total dosages of from 500,000 units to 4,800,000 units. However, as recent articles in *The Journal of the American Medical Association*[1] have pointed out,

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This work was done in cooperation with the Pediatric Departments of the Washington University School of Medicine and the St. Louis City Hospital. Serologic studies were done at the Snodgras Laboratory division of the St. Louis City Hospital.

The majority of the patients were treated at the Midwestern Medical Center, United States Public Health Service Rapid Treatment Hospital, St. Louis.

1. Platou, R. V.; Hill, A. J.; Ingraham, N. R.; Goodwin, M. S.; Wilkinson, E. E., and Hausen, A. E.: Penicillin in the Treatment of Intantile Congenital Syphilis, J. A. M. A. **127**:582 (March 10) 1945.

probably the larger doses are more efficacious. The average dose for adults has been 1,200,000 or 2,400,000 units, and the latter has seemed the better. Our average dose for children now is 1,200,000 units, and if the weight dose relationship of children is comparable to that of adults certainly the children are receiving many times the average adult dose.

I. DIAGNOSIS

21 Cases of Congenital Syphilis

7 Cases of Acquired Syphilis

The patients with congenital syphilis varied in age between 2½ months and 9 years. The larger proportion were less than 1 year of age. Those with acquired syphilis varied from 5½ months to 10 years of age. All were previously untreated.

Thirteen of the patients with congenital syphilis were in the infectious stage. In 5 of these 13 spirochetes were observed on dark field examination. In all cases a diagnosis of syphilis in the mother was established. For the other 8 patients with congenital syphilis, a diagnosis was established by serologic changes, roentgenologic evidence of osseous syphilis and other stigmas in addition to the establishment of the diagnosis of syphilis in the mother.

For the 7 patients with acquired syphilis, the diagnosis was established by the presence of positive dark field–condylomas in 3 cases, typical chancre in 1 case, morphologically typical secondary lesions in 2 cases (in 1 of which spirochetes were found on dark field examination) and a valid history and serologic reactions in the seventh case.

Eleven of the 39 patients have been treated so recently that we are not reporting on them at this time. Our reportable series, therefore, consists of 28 cases which have been followed for a minimum of two months after treatment. Data for this series of cases is presented in table 1.

II. DOSAGE

Early investigators on this problem used as a base line a total dose of 20,000 units of penicillin per kilogram of body weight. This corresponded to a 1,200,000 unit total dose for an adult. Platou, Hill, Ingraham and their co-workers employed a total of 16,000 to 32,000 units per kilogram body weight. Even more recently a medical directive issued March 24, 1945 by the Venereal Disease Division, United States Public Health Service, recommends a total dose of 40,000 units per kilogram of body weight.

Early experience led us to feel that these smaller total doses were inadequate. Our first patients were treated with a total dose of 500,000 units. Serologic response was unsatisfactory, the titer showing an

TABLE 1.—*Serologic Titer of Blood of Twenty-Eight Patients After Treatment at Monthly Intervals*

Patient	Age	Diagnosis	Total Dose Penicillin Units	Serologic Titer Kahn Units													
				Initial	1 Mo.	2 Mo.	3 Mo.	4 Mo.	5 Mo.	6 Mo.	7 Mo.	8 Mo.	10 Mo.	11 Mo.	14 Mo.	15 Mo.	16 Mo.
D. S.	3 mo.	Cong.	1,500,000	360	...	..	4	4	1	..	Neg.	Neg.	..	..	Neg.	..	..
J. A. M.	2½ mo.	Cong.	1,500,000	360	...	..	80	40	4	..	1	1	Neg.	Neg.	..	4*	Neg.
D. M.	2¾ mo.	Cong.	1,900,000	360	120	40	..	3	..	Neg.	..	..	..	..	..	..	..
R. D.	4 mo.	Cong.	500,000	360	280	Lost	..	..	..	..	..	..	..	..	..	..	..
L. L.	4 yr.	Cong.	1,500,000	360	360	Lost	..	..	..	..	..	..	..	..	..	..	..
R. S.	16 mo.	Cong.	1,810,000	120	40	20	40	..	..	2†	..	..	..	..	..	..	..
W. E. F.	15 mo.	Cong.	1,500,000	360	280	..	..	..	40	..	40	40	..	..	..	..	..
M. F.	4 mo.	Cong.	500,000	360	120	40	Lost	..	..	..	..	..	..	..	..	..	..
R. C.	6 wk.	Cong.	1,200,000	280	40	..	..	3	2	Neg.	..	..	..	..	..	..	..
W. G.	2 yr.	Cong.	1,200,000	360	...	..	..	80	..	..	..	..	..	..	..	..	..
R. W.	3 mo.	Cong.	1,200,000	360	120	40	3	1	Neg.	..	..	..	..	..	..	..	..
B. F. M.	4 mo.	Cong.	1,200,000	360	...	..	..	40	..	..	..	..	..	..	..	..	..
R. H.	19 mo.	Cong.	1,200,000	3	4	2	3	..	..	..	..	..	..	..	..	..	..
E. P.	5 mo.	Acq.	1,200,000	4	360	240	80	20	..	4	..	..	..	..	..	..	..
S. R.	4½ yr.	Acq.	1,000,000	80	80	Neg.	..	Neg.	Neg.	..	..	..	..	..	..	..	..
L. C.	5½ yr.	Acq.E.Lat.	1,500,000	120	40	4	4	3	Neg.	..	Neg.	..	..	Neg.	..	..	..
W. A. F.	4 yr.	Acq.	800,000	200	120	120	..	..	..	..	..	..	Lost	..	..	..	..
R. D. B.	1 day	Cong.	720,000	200	Died 8 days after therapy; serologic titer at that time was 40.												
E. B.	9 mo.	Cong.	2,400,000	160	120	..	40	..	..	..	..	..	..	..	..	..	..
J. W.	19 mo.	Cong.	1,800,000	80	120	..	40	..	..	..	..	..	..	..	..	..	..
S. T.	5 mo.	Cong.	1,200,000	720	640	160	..	..	..	..	..	..	..	..	..	..	..
S. W.	4 yr.	Cong.	1,500,000	200	320	..	200	..	..	..	..	..	..	..	..	..	..
D. W.	22 mo.	Cong.	1,200,000	320	720	600	..	..	..	..	..	..	..	..	..	..	..
G. M.	10 yr.	Acq.	1,800,000	240	160	40	20	4	..	..	..	..	..	..	..	..	..
B. A.	7½ mo.	Cong.	1,200,000	200	40	40	20	..	..	..	..	..	..	..	..	..	..
M. W.	4½ yr.	Acq.	1,200,000	160	Dbtful.	Dbtful.	..	..	..	..	..	..	..	..	..	..	..
V. W.	28 mo.	Acq.	1,200,000	320	Dbtful.	Dbtful.	..	..	..	..	..	..	..	..	..	..	..
J. B	32 mo.	Cong.	1,200,000	280	Pos.	Pos.	..	..	..	..	..	..	..	..	..	..	..

* Doubtful Wassermann reaction.
† Negative Wassermann reaction.

initial rapid drop followed by a great increase in ten days and remaining at a high level maintained for thirty days. We therefore administered another course of 500,000 units, with no appreciable serologic response. A third 500,000 units, however, given two months after the initial therapy, was followed by a complete reversal of the serologic response. This patient had a diagnosis of florid secondary syphilis. A second case was similar in serologic response and type of treatment. Accordingly, our total dose has ranged from 80,000 to 300,000 units per kilogram of body weight, the majority of the children receiving an average dose of 100,000 to 125,000 units per kilogram. Time alone will decide whether these larger doses are more effective than the smaller doses hitherto used.

Time Interval.—Cooke and Goldring's work has indicated that it is highly possible that the three hour time interval is too great for maximal therapeutic efficiency, inasmuch as this interval does not permit a maintenance of high constant level of penicillin in the blood stream. These authors pointed out that the highest level of penicillin in the blood is obtained from thirty minutes to one hour after injection and the level drops rapidly during the second hour with subcutaneous or intramuscular routes of administration.

In our earlier cases we felt that larger doses should have been given, but at that time penicillin was difficult to obtain and little or nothing was known as to how the drug would be tolerated in large doses by infants with syphilis.

According to Rammelkamp and Keefer,[2] three hours has been generally conceded to be the most practical and desirable time interval between injections, in order to maintain an adequate blood penicillin level. In 3 instances, subcutaneous administration was resorted to, based on penicillin absorption curves derived by Cooke and Goldring.[3] Also on the basis of their work, the time interval was reduced.

The total dosage was determined by two factors: (1) available penicillin, and (2) an effort to determine an effective weight dose relationship. Experimentally, in 2 cases a one hour interval was resorted to; in 1 case a two hour interval and in 1 case a four hour interval were used. In all other cases the patients were treated with a three hour interval between treatments. The individual dose varied from 10,000 (average) to 25,000 units. Some of the infants were given injections of 2,500 to 5,000 units, to minimize the possibility of a severe Herxheimer reaction.

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2. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Distribution of Penicillin, J. Clin. Investigation **22**:425 (May) 1943.

3. Cooke, J. V., and Goldring, D.: The Concentration of Penicillin in Body Fluids, J. A. M. A. **127**:80 (Jan. 13) 1945.

III. RESULTS

These children have been followed to date at monthly intervals whenever possible. Several of these children live in remote communities, and it has been difficult and sometimes impossible to obtain a satisfactory follow-up. The present status of the group is shown in table 1. The results are condensed in table 2.

TABLE 2.—*Résumé of Results*

Lost to observation	4
Died	1
Free from syphilis (clinically and serologically)	7
With titer of less than 4 Kahn units	6
Still strongly positive for syphilis (9 with declining Kahn titer)	10
Total	28

IV. COMMENT

It is far too early to attempt any conclusive evaluation of the role of penicillin in the treatment of syphilis in children. However, certain striking effects on the child and on the disease are apparent:

1. The spirochete disappeared rapidly from local lesions, within four to eight hours no viable organisms being found.

2. The lesions healed rapidly and completely. Snuffles cleared rapidly but not as rapidly as cutaneous and mucous membrane lesions.

3. In our 3 cases, syphilitic periostitis disappeared clinically in approximately one month, and serial roentgenologic studies showed decided and progressive healing in two to three months. In three months no evidence of bony syphilis could be found.

4. Herxheimer reactions occurred in 9 instances.

5. Progressive decline in serologic titer was noted in all but 1 case in this series. In this 1 case, the titer declined at first but has remained stationary for several months. In this instance, treatment may have to be classed as failure.

6. There was a definite improvement of the child's nutritional state both during and after penicillin therapy.

7. The therapy did not interfere with the taking or retention of foods in infants.

8. In no case was infection at the site of injection observed.

9. Initial changes in the spinal fluid findings were encountered in 2 cases. In 1 of these a post-treatment spinal fluid examination was made. The serologic reaction of the spinal fluid in this case had declined from 20 to 4 Kahn units. The colloidal gold curve, total protein level and

cell counts both before and after treatment in this case were within normal limits.

10. There were no evidences of a Milian reaction or secondary fever.

11. In no case did we see an allergic reaction.

12. One fatality occurred in this series. We present herewith a summary of this case.

REPORT OF A CASE

R. DeB., a Negro girl, was admitted to St. Louis Children's Hospital on Oct. 17, 1944, at 24 hours of age, with chief complaints of a rash and dyspnea of eighteen hours' duration.

Family History.—The mother, aged 19, and the father, aged 21, were living and well. Each gave a history of having negative Kahn reactions of the blood nine months previously. Both, however, had strongly positive Kahn reactions at the time of the infant's admission.

Present Illness.—The patient was a full term baby born after a six hour labor, with spontaneous cry and respiration. The cry was feeble, however, and the baby then remained quiet and seemed drowsy. She was observed to breathe irregularly.

Physical Examination.—The temperature was 37 C. (98.6 F.) and the weight 2,850 Gm. The baby was acutely ill, the cry feeble and the respirations grunting in type. The mucous membranes were icteric, and the skin was covered with a purpuric eruption with areas ranging up to 1 cm. in diameter and roughly circular. The superficial layers of the skin were desquamating, and there was no thickening of the skin of the palms or soles. The eyes showed decided icterus of the scleras. There were many petechiae on the mucous membranes. The chest was symmetric and the percussion note resonant bilaterally. Over the bases of both lungs the breath sounds were diminished, and fine crackling rales were present. Examination of the abdomen revealed a greatly enlarged spleen, which was palpable at the level of the umbilicus. The Moro reflex was active. The remainder of the physical examination revealed normal conditions.

Laboratory Data.—On entry the urine was normal. The hemogram showed a hemoglobin level of 12.4 Gm. and 35,340 leukocytes per hundred cubic centimeters with a decided left shift in the Shilling differential count. A few erythroblasts and normoblasts were also present in the smear. Kline, Kahn and Wassermann reactions were all positive. The bleeding time was five minutes and the clotting time four and one-half minutes. Clot retraction was poor in twenty-four hours.

Two days later the hematology department of the Washington University School of Medicine reported on the peripheral blood as follows: red cell count, 2,150,000; hemoglobin level, 7.0 Gm.; reticulocytes, 15.3 per cent; leukocytes, 16,450, and platelets, 10,750 (normal, 400,000 to 800,000). The differential count showed: eosinophils, 1 per cent; myelocytes, 4 per cent; metamyelocytes, 3 per cent; band cells, 10 per cent; segmented cells, 30 per cent; lymphocytes, 40 per cent, and monocytes, 12 per cent; there were 3 normoblasts to 100 leukocytes. There were decided anisocytosis and poikilocytosis. This picture was thought compatible with thrombopenic purpura and chronic hemorrhage. It was not compatible with erythroblastosis fetalis.

An examination of the tibial bone marrow was then performed, and the observations were reported as follows: eosinophils, 8 per cent; myelocytes C, 29 per cent;

myelocytes B, 8 per cent; myelocytes A, 5 per cent; metamyelocytes, 16 per cent; band forms, 16 per cent; segmented cells, 5 per cent; lymphocytes, 1 per cent, and monocytes, 0. There were 3 per cent phagocytic clasmatocytes, 13 per cent primitive forms and 0.5 per cent reticulum cells. In counting nucleated red blood cells, in 100 leukocytes there were found 63 normoblasts, 24 late erythroblasts and 11 early erythroblasts, a total of 98. No normal mature megakaryocytes were seen. An occasional cell was seen which might have been a very young megakaryocyte. The marrow was thought to be normal but for two features: 1. There was a definite erythroid stimulation, many more normoblasts and erythroblasts being present than are seen in normal bone marrow. This was thought to be due to chronic hemorrhage. 2. The absence of normal megakaryocytes was thought to establish the diagnosis of secondary thrombopenic purpura. "The primary agent which has exerted a toxic effect on the megakaryocytes could be either (*a*) a toxic agent perhaps circulating in the mother's blood during her pregnancy or (*b*) destruction of the megakaryocytes might possibly be the result of syphilis of the bone."

Roentgenograms of long bones were reported as follows: "There is a peculiar lack of calcification at the distal ends of the shafts of all long bones of the body visualized. On the femur the area appears to be about 1.5 to 2 cm. long at each end. The midportion of the shaft is of normal mineral content. The trabecular formation in the distal end appears normal. The epiphyses appear normal. Similar changes are found in the long bones of the arm and forearm on each side and in the metacarpal bones of the right hand, which can be seen on this film. The disturbance appears to be one of a diminished deposition of calcium in the growing bones during intrauterine life rather than a decalcification. This may well be the result of congenital syphilis."

Lumbar puncture ten days after entry yielded fluid which was blood-tinged and xanthochromic, and contained 12 cells. The Wassermann reaction of the spinal fluid was positive, but it was thought to be so because of the bloody tap. Eleven days later the lumbar puncture was repeated, and clear xanthochromic fluid was obtained which gave a negative Wassermann reaction.

Course in Hospital.—The course was gradually downhill. The midline abdominal mass disappeared and was never explained. The baby did not eat well; the temperature remained normal, and anemia recurred repeatedly; it was corrected by transfusions of whole blood, only to recur. The icterus became severe, and twelve days after entry the icterus index was 250. The petechiae cleared spontaneously, and no other bleeding points were found. However, the platelet count remained low.

Penicillin therapy for congenital syphilis was begun on the baby's fourteenth day in the hospital. The drug was administered subcutaneously, 5,000 units every three hours; 720,000 units were administered prior to the baby's death, over a period of eight days. The temperature was normal the first two days, and the baby did well. On the third day the temperature spiked to 39.6 C., and from then on it continued to range between 37.5 and 40 C. until death, four days later. No actual cause for the fever could be demonstrated. Cultures of blood were repeatedly sterile, and there was no leukocytosis. However, on a postmortem culture of heart blood there grew Streptococcus viridans. After therapy was begun, platelet counts were made each day grossly by counting the number in 100 leukocytes. They increased from 50 in 100 leukocytes to 450 in 100 leukocytes. Twenty-four hours prior to the baby's death, a mass appeared in the right lower quadrant of the abdomen, but the nature of the mass was not determined. Stools remained normal, and there was no vomiting. Abdominal distention occurred, and a few

hours later, following a feeding, the baby vomited, apparently aspirated vomitus and, despite artificial respiration and other emergency procedures, died. It was impossible to obtain permission for postmortem examination.

Diagnoses.—The diagnoses were: (1) congenital syphilis; (2) toxic thrombocytopenic purpura, possibly due to syphilis; (3) question of delayed Herxheimer reaction, and (4) question of septicemia due to Streptococcus viridans.

It is difficult to evaluate this case or to state positively whether death could in any way be ascribed to the antisyphilitic therapy with penicillin.

SUMMARY

1. Thirty-nine children and infants with syphilis have been treated with penicillin.

2. Twenty-eight cases have been followed from two to sixteen months.

3. Seven patients are clinically and serologically free from syphilis.

4. Six patients are clinically free from syphilis and serologically show a titer of less than 4 Kahn units.

5. Ten patients have strongly positive serologic reactions, but 9 of those show a declining serologic titer of the blood. These 9 patients have shown clinical improvement.

6. One patient has shown no improvement in blood serologic titer for three months.

7. One death occurred during penicillin therapy.

OPTIMAL ZONE REACTION IN THE DIAGNOSIS AND TREATMENT OF SYPHILIS

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A PRELIMINARY report is herewith presented of a supplementary serologic procedure to serodiagnostic tests. This procedure, referred to as optimal zone procedure, is applicable to known cases of syphilis. When applied to such cases, it gives promise to be of value: (1) in supporting the diagnosis of clinically positive, seronegative syphilis; (2) in providing an index of cure in syphilis more dependable than serodiagnostic tests, especially in evaluating rapid methods of treatment, and (3) in demonstrating different precipitation patterns in different situations in syphilis—patterns which give indication of having clinical significance.

1. BASIS OF OPTIMAL ZONE PROCEDURE

The optimal zone procedure is based on an extension of the serum: antigen ratios from three, employed in the standard Kahn test, to ten and, in some cases, fifteen ratios. Twenty years ago,[1] when my interest was directed to the principles governing the phenomenon of precipitation in syphilis which laid the foundation for the standard Kahn test, I reported that for optimal precipitation results it is necessary to employ appropriate serum: antigen ratios. I then employed a range of serum: antigen ratios of 1:2, 1:1, 1.5:1, 2:1, 3:1, 6:1, 12:1 and 24:1 and observed that the stronger the reacting capacity of the serum the greater the tendency toward positivity with increasing amounts of antigen while the weaker the reacting capacity of the serum the greater the tendency toward positivity with decreasing amounts of antigen. This observation led me at first to consider the use of six or more serum: antigen ratios for a serodiagnostic test, but for reasons of greater practicability in routine blood testing the use of three serum: antigen ratios, namely 3:1, 6:1 and 12:1, was decided on. These three ratios, employed in the standard Kahn test, strike a good average of serologic reactivity for a serodiagnostic test in the majority of

From Clinical Laboratories, University Hospital, University of Michigan.

1. Kahn, R. L.: (*a*) Serum Diagnosis of Syphilis by Precipitation, Baltimore, Williams & Wilkins Company, 1925, p. 54; (*b*) The Kahn Test: A Practical Guide, ibid., 1928, p. 17.

cases of syphilis, but to determine optimal serologic reactivity in certain cases an extension of these ratios is necessary.

The relationship between the standard Kahn and optimal zone technics is presented in table 1. Ten serum : antigen ratios are employed : namely, 1 : 1, 2 : 1, 3 : 1, 6 : 1, 12 : 1, 24 : 1, 36 : 1, 48 : 1, 76 : 1 and 100 : 1. For simplicity, these ratios are divided into three zones. Zone II represents the ratios employed in the standard Kahn test; zone I consists of ratios in which the antigen is increased in relation to the serum, and zone III consists of ratios in which the serum is increased in relation to the antigen. The precipitation results are recorded as negative (–), doubtful (±), 1 plus (1), 2 plus (2), 3 plus (3), 4 plus (4), depending on the degree of precipitation.

TABLE 1.—*Illustrative Patterns of Optimal Zone Reaction*

	Serum : Antigen Suspension									
	Zone I		Zone II (Standard Kahn)			Zone III				
Serologic Pattern Number	1:1	2:1	3:1	6:1	12:1	24:1	36:1	48:1	76:1	100:1
	Optimal Precipitation with Increase of Antigen over Serum									
1	4	4	1	—	—	—	—	—	—	—
	4	4	4	4	4	4	1	—	—	—
	4	4	4	4	4	4	4	1	—	—
	Optimal Precipitation with Moderate Amounts of Serum and Antigen									
2	—	—	—	1	4	2	1	—	—	—
	—	—	1	4	4	4	1	—	—	—
	—	1	4	4	4	4	4	1	—	—
	Optimal Precipitation with Increase of Serum over Antigen									
3	—	—	—	—	—	—	—	4	4	4
	—	—	—	—	1	4	4	4	4	4
	—	—	4	4	4	4	4	4	4	4
	Precipitation in All Ratios									
4	4	4	4	4	4	4	4	4	4	4
	Negative in All Ratios									
5	—	—	—	—	—	—	—	—	—	—

Four serologic patterns are illustrated in the table. In pattern 1, optimal precipitation is noted in zone I, in which the antigen is increased in relation to the serum. In pattern 2, optimal precipitation is noted in zone II or on the borders of zones II and III, in which the amounts of antigen and serum are not noticeably increased over one another. In pattern 3, optimal precipitation is noted in zone III, in which the serum is increased over the antigen. In pattern 4, precipitation is noted in all ratios.

2. OPTIMAL ZONE REACTION IN SUPPORTING THE DIAGNOSIS OF CLINICALLY POSITIVE SERONEGATIVE SYPHILIS

The occasional occurrence of seronegative reactions in the presence of syphilis has remained an anomaly in the serologic behavior of this

disease. Considering the high sensitivity of modern serodiagnostic technics, it might have been expected that seropositivity would be attained in all known cases of syphilis. Actually, seronegativity is encountered in the presence of syphilis not only with serodiagnostic tests but also with supersensitive tests, such as the Kahn presumptive and Kline exclusion technics. "Seronegative syphilis" has indeed become a commonplace term in clinical medicine, and clinicians and serologists have long emphasized that a negative reaction to serodiagnostic tests does not eliminate the possibility of syphilitic infection. What is particularly anomalous is the fact that the same serodiagnostic tests which elicit negative reactions in certain known cases of syphilis elicit positive reactions in certain cases in the absence of this disease;

TABLE 2.—*Cases of Syphilis Showing Optimal Precipitation in Zone I or III and not in the Serum:Antigen Range of the Standard Kahn Test*

Case No.	Serum : Antigen Suspension										Clinical History of Syphilis
	Zone I		Zone II (Standard Kahn)			Zone III					
	1:1	2:1	3:1	6:1	12:1	24:1	36:1	48:1	76:1	100:1	
1	—	—	—	—	1	4	4	4	4	4	Primary
2	—	—	—	—	—	4	4	2	1	1	Primary
3	—	—	—	—	—	3	2	±	—	—	Primary
4	—	—	—	—	—	4	4	4	3	3	Early latent
5	—	—	—	—	—	4	4	4	2	1	Early latent
6	4	3	1	—	—	—	—	—	—	—	Congenital
7	4	4	±	—	—	—	—	—	—	—	Congenital
8	4	4	2	—	—	—	—	—	—	—	Congenital
9	4	4	1	—	—	—	—	—	—	—	Neurosyphilis
10	4	4	3	—	—	—	—	—	—	—	Neurosyphilis

for it would seem reasonable to believe that serodiagnostic tests, so sensitive as to give "false positive" reactions, would be free from "false negative" reactions.

Among the explanations generally offered for seronegativity in cases of syphilis are: that the host is incapable of producing antibodies; that the blood serum contains an inhibitory substance, and that the colloidal state of the serum masks reactivity with the antigen. Studies on optimal zones of reactivity in the serology of syphilis indicate that the occurrence of at least certain false negative reactions with modern serodiagnostic tests is due to the limited serum: antigen ratios employed in these tests. Table 2 presents data of 10 cases of syphilis in which the optimal precipitation zone is outside the serum: antigen range of the standard Kahn test. It is evident that persons with syphilis may show optimal precipitation in zone III and no precipitation in zones I and II while others may show optimal precipitation in zone I and very weak or no precipitation in zone II. Thus, in a certain percentage of cases

of syphilis negative reactions may be obtained with a serodiagnostic test, not because the patients are truly seronegative but because the serum : antigen ratios employed in the test are not optimal for these patients.

All serodiagnostic tests, whether precipitation or complement fixation, to my knowledge, employ single ratios of serum to antigen, with the exception of the standard Kahn test, which, as already indicated, employs three ratios. Actually, a test employing one ratio of serum to antigen can easily be as sensitive as, or more sensitive than, a test employing three ratios; all that is necessary is the use of an antigen of sufficiently high sensitivity. Thus, the presumptive Kahn procedure, which employs a single ratio of serum to antigen, is about 10 per cent more sensitive than the standard Kahn test, owing to the increased sensitivity of the antigen. As the sensitivity of the antigen is increased, the optimal zone of precipitation with different serum : antigen ratios widens but the basic serologic pattern remains the same. Hence, when serodiagnostic tests or supersensitive tests elicit negative reactions in known cases of syphilis, it can mean only that the reactions are negative in the serum : antigen ratios employed and it is possible that positive reactions would be obtained in other serum : antigen ratios.

Based on these considerations, it becomes understandable why modern serodiagnostic tests may elicit negative reactions in certain cases of syphilis and yet elicit positive reactions in the absence of the disease. The explanation appears to be that the limited serum : antigen ratios of serodiagnostic tests may not be optimal for certain cases of syphilis and may be optimal for certain nonsyphilitic cases. It is not claimed that the optimal zone procedure will elicit positive reactions in all cases of syphilis in which serodiagnostic tests elicit negative reactions. Only prolonged trial can indicate the extent to which this procedure will elicit positive reactions in such cases. That it elicits positive reactions in some of these cases is evident from the data presented in this article.

3. OPTIMAL ZONE REACTION IN THE ESTABLISHMENT OF CURE FOLLOWING THERAPY IN SYPHILIS

It is common knowledge that seronegativity following therapy cannot be taken as a criterion of cure. This is understandable. For as long as seronegativity is encountered in certain cases in the presence of syphilis, seronegativity following therapy might also occur in the presence of the disease. If it were possible to have a serologic procedure which would be able to detect nearly all cases of syphilis, negativity following therapy could, with reasonable certainty, be accepted as a criterion of cure. Hence, to the extent to which the optimal zone procedure will prove effective in the detection of syphilis in all its

manifestations, it will prove similarly effective as a criterion of cure following therapy.

In the evaluation of the rapid methods of treatment, it would seem particularly desirable to apply the optimal zone procedure. The prolonged follow-up system necessary with the use of present day serodiagnostic tests is well known and is important as an aid in the detection of relapses. But relapses can mean only that the patients under observation have never been cured; hence, they may never have been truly seronegative. They merely became negative with serodiagnostic tests, which is equivalent to being negative in the particular serum: antigen ratios employed in these tests. They might have shown positivity in certain serum: antigen ratios of the optimal zone procedure.

There is obviously great need for a serologic criterion of cure in syphilis. It is clear that any such criterion will have to undergo extensive and prolonged trial. Considering, however, the time and expense necessary to follow up a patient who, let us say, had undergone one of the rapid methods of treatment, the use of an elaborate serologic method such as the optimal zone procedure seems justifiable.

OPTIMAL ZONE REACTION IN THE DEMONSTRATION OF DIFFERENT PRECIPITATION PATTERNS IN DIFFERENT SITUATIONS IN SYPHILIS

In 1923[2] I reported different precipitation trends with the three serum: antigen ratios of the standard Kahn test (table 3). In some

TABLE 3.—*Typical Precipitation Reactions with Four Different Serums*

Serum	Serum : Antigen Suspension 3:1	6:1	12:1	Clinical Diagnosis
1	4	4	4	Hunterian chancre, early secondary
2	4	2	—	Probably latent, untreated
3	±	2	4	Intensively treated
4	—	—	—	Free from syphilis

Adapted from Kahn.[2]

instances complete precipitation was noted in all three ratios; in others complete precipitation was noted only in the ratio in which the serum was increased in relation to the antigen; in still others complete precipitation was noted only in the ratio in which the serum was reduced in relation to the antigen. This observation gave some indication of the existence of different serologic patterns in syphilis. To elicit these patterns fully, however, it was necessary to employ an extensive serum: antigen range.

2. Kahn, R. L.: Rapid Precipitation Phase of the Kahn Test for Syphilis, J.A.M.A. **81**:88 (July 14) 1923.

Table 4 presents the four precipitation patterns of the optimal zone reaction in 24 cases of syphilis in which the patients have undergone various degrees of therapy. Pattern 1, in which optimal precipitation occurs with excess of antigen in relation to serum (zone I), is noted most frequently in late syphilis, less frequently in early syphilis. Pattern 2, in which optimal precipitation occurs with moderate amounts of serum and antigen (zone II), is noted most frequently in cases of treated syphilis both early and late. Pattern 3, in which optimal precipitation occurs with excess of serum in relation to antigen (zone III), is noted frequently in early syphilis and least frequently in late syphilis. Pattern 4, in which precipitation is noted in all serum: antigen ratios, may occur apparently in all stages of syphilis, especially of untreated or of little treated syphilis.

TABLE 4.—*Optimal Zone Reactions in Different Cases of Syphilis*

	Serum : Antigen Suspension										
	Zone I		Zone II (Standard Kahn)			Zone III					
Case No.	1:1	2:1	3:1	6:1	12:1	24:1	36:1	48:1	75:1	100:1	Clinical Diagnosis of Syphilis
	Optimal Precipitation with Increase of Antigen over Serum										
1	4	4	4	1	—	—	—	—	—	—	Late latent
2	4	4	4	4	4	4	—	—	—	—	Late latent
3	4	4	4	4	4	2	1	—	—	—	Late latent
4	4	4	4	4	4	2	—	—	—	—	Late latent
5	4	4	4	4	4	4	4	4	—	—	Early latent
6	4	4	4	4	4	4	3	3	2	1	Secondary
	Optimal Precipitation with Moderate Serum : Antigen Amounts										
7	—	—	—	±	3	1	—	—	—	—	Early latent
8	—	—	—	±	3	2	2	—	—	—	Early latent
9	—	—	—	1	4	4	4	—	—	—	Late latent
10	—	—	—	2	4	4	4	3	—	—	Late latent
11	—	—	—	4	4	4	4	3	—	—	Tabes
12	—	4	4	4	4	4	4	2	1	1	Secondary
	Optimal Precipitation with Increase of Serum over Antigen										
13	—	—	—	—	1	3	4	4	4	4	Primary
14	—	—	—	—	—	4	4	4	4	2	Primary
15	—	—	—	4	4	4	4	4	4	4	Primary
16	—	1	4	4	4	4	4	4	4	4	Primary
17	—	4	4	4	4	4	4	4	4	4	Secondary
18	—	—	2	4	4	4	4	4	4	4	Late latent
	Precipitation in All Ratios										
19	3	4	4	4	4	4	4	4	4	4	Primary
20	4	4	4	4	4	4	4	4	4	4	Secondary
21	4	4	4	4	4	4	4	4	4	4	Secondary
22	4	4	4	4	4	4	4	4	4	4	Early latent
23	4	4	4	4	4	4	4	4	4	4	Late latent
24	4	4	4	4	4	4	4	4	4	4	General paresis

The significance of the different precipitation patterns in the diagnosis and treatment of syphilis can be determined only if these patterns are observed in the same patients before, during and after therapy. Thus, 2 patients with the primary stage of syphilis may have positive reactions with serodiagnostic tests and precipitation readings of

– – 2 4 4 4 4 4 4 4 with the optimal zone procedure. In the course of several months, after having been treated by one of the rapid methods, the patients have negative reactions with serodiagnostic tests. But with the optimal zone procedure the patients show some serologic activity, patient 1 having precipitation readings of – – – – 1 4 3 – – – and patient 2 showing readings of 4 2 – – – – – – – – –. These precipitation readings indicate decided differences in the serologic response of these 2 patients to the therapy. Patient 1 exhibits a serologic picture common in cases of treated syphilis approaching negativity. The antibody concentration of the serum is low, and positivity can be demonstrated only in a narrow range of serum : antigen ratios, apparently optimal in the middle zone. This residual positivity may spontaneously disappear in the course of a month or two, the patient becoming completely seronegative; or it may flare up as a result of a clinical relapse. Patient 2, on the other hand, exhibits a serologic picture common in late syphilis. Precipitation is noted only in the first two ratios of the optimal zone procedure, presumably because the serum is especially rich in antibodies and hence reacts only with the large amounts of antigen present in these ratios. The negative readings in the remaining eight ratios are due to the disproportionate amounts of antibodies and antigen in these ratios : namely, very high concentration of antibodies and low concentration of antigen. If the concentration of antibodies is reduced by diluting the serum with isotonic solution of sodium chloride, positive precipitation will be obtained in these ratios. Patient 2, with this serologic response, is not likely to become seronegative spontaneously, and he may indeed need extraordinary therapeutic measures. Obviously, the full significance of each of the four serologic patterns in the diagnosis and treatment of syphilis can become evident only after extensive trial.

It should be emphasized that the optimal zone procedure is not a serodiagnostic test to aid physicians in the establishment of a diagnosis of syphilis. As already pointed out, it is applicable only to cases in which a diagnosis of syphilis has already been established. Also, the optimal zone procedure is of no value in the detection of false positive reactions, for which my verification test [3] is employed in this laboratory. The extent to which the procedure gives different serologic patterns with various animal (pig, horse, rabbit and other) serums is under investigation in this laboratory. Thus far it has been observed that certain of these serums show precipitation in all ten serum : antigen ratios and that others show optimal precipitation in zone III, in which the serum is in excess of antigen.

3. Kahn, R. L.: Technique of the Standard Kahn Test and of Special Kahn Procedures, Ann Arbor, University of Michigan Press, 1946, p. 31.

5. QUANTITATIVE OPTIMAL ZONE REACTION

Quantitive optimal zone determinations are carried out by making serial dilutions of serum with isotonic solution of sodium chloride and employing these dilutions in each of the serum: antigen ratios of the optimal zone procedure; the highest dilution of serum showing precipitation is the optimal quantitative titer. Present day quantitative serologic procedures are based on a single ratio of serum to antigen. This ratio may or may not give the optimal quantitative titer in a given case. Thus, in a syphilitic person giving an optimal zone reaction, let us say, of – – 4 4 4 2 – – – –, the routine quantitative Kahn procedure, employing a 6: 1 ratio of serum: antigen, is likely to give the optimal quantitative titer. But for a syphilitic person giving an optimal zone reaction of – – – – – – 2 4 4 4, the 6: 1 serum: antigen ratio is not applicable, as it lies within the zone of seronegativity and any quantitative determination in that ratio is likely to give negative results. In this case, a quantitative test performed with a serum: antigen ratio of 76: 1 might give the optimal quantitative titer.

In the early years of the Kahn reaction, I considered the use of three serum: antigen ratios in the diagnostic test and eight or ten ratios in the quantitative test.[4] Hopkins and Rockstraw [5] and Wilson, Kurtz and Larkum [6] also suggested the use of increased serum: antigen ratios over the three ratios of the diagnostic test for quantitative determinations. The main difficulty with the use of multiple serum: antigen ratios in a quantitative procedure was the requirement of a relatively large amount of serum, such as 2 cc. I chose instead a quantitative procedure, since known as the quantitative Kahn procedure, based on serial dilutions of serum with isotonic solution of sodium chloride, for which relatively minute amounts of serum, such as 0.1 or 0.2 cc., are sufficient.

It is not recommended that quantitative optimal zone determinations replace the quantitative Kahn procedure in the routine follow-up of treated patients. The simplicity of the latter procedure and its basic value in the majority of cases make it preferable for routine use. The clinical value of the quantitative optimal zone procedure is under investigation.

6. TECHNIC OF OPTIMAL ZONE PROCEDURE

The technic of the optimal zone procedure is outlined in table 5. It will be noted that the serum and the antigen suspension in zone II are employed in micro amounts. The antigen suspension is measured with a 0.1 cc. pipet graduated in 0.001 cc. The serum in amounts up

4. Kahn,[1b] p. 132.

5. Hopkins, J. G., and Rockstraw, E. W.: Quantitative Determination of the Kahn Reaction, J. Lab. & Clin. Med. **13**:146 (Nov.) 1927.

6. Wilson, D.; Kurtz, M. B., and Larkum, N. W.: The Zone of Precipitation in the Kahn Test, Am. J. Syph. & Neurol. **18**:355 (July) 1934.

to 0.2 cc. is measured with a 0.2 cc. pipet graduated in 0.001 cc., and in amounts over 0.2 cc. with a 1 cc. pipet graduated in 0.01 cc. The isotonic solution of sodium chloride is also measured with a 1 cc. pipet, or if desired, with a 2 cc. pipet. The technical steps are the same as those employed in the standard Kahn test.

The types of reactions noted are illustrated in table 1. In reporting to physicians, it seems best to report the readings in all ten tubes. Thus, when all tubes show a 4 plus precipitation, the report should read 4 4 4 4 4 4 4 4 4 4, and when none of the tubes show precipitation the report should read – – – – – – – – – –. It is evident that tubes 3, 4 and 5 in the series contain the serum : antigen ratios employed in the Kahn test.

The optimal zone procedure, while consisting of ten ratios of serum : antigen, need not be limited to that number of ratios; additional

TABLE 5.—*Technic of Optimal Zone Procedure*

Serum : Antigen Suspension									
Zone I		Zone II (Standard Kahn)			Zone III				
1:1	2:1	3:1	6:1	12:1	24:1	36:1	48:1	76:1	100:1
Standard Antigen Suspension, Cc.									
0.05	0.05	0.02	0.01	0.01	0.01	0.005	0.005	0.005	0.005
Serum, Cc.									
0.05	0.1	0.06	0.06	0.12	0.24	0.18	0.24	0.38	0.5
0.9% NaCl Solution, Cc.									
1.0	1.0	0.4	0.4	0.3	0.2	0.25	0.2	0.1	0

The tubes are shaken for three minutes, and the results are read after the addition of salt solution.

ratios, such as 1 : 2 and 1 : 3 and 150 : 1 and 200 : 1, might be employed in some cases. Studies are in progress to determine the value of sensitized antigen (of the presumptive test) in the optimal zone procedure.

Indications are that only antigens having "sloping"[7] titers are suitable in eliciting different precipitation patterns with the optimal zone reaction and that antigens having "flat" titers are not suitable. Antigens having sloping titers show titration pictures of increasing clarity with the increase in the amounts of isotonic solution of sodium chloride in the preparation of the antigen suspensions. Antigens having flat titers show titration pictures of similar clarity with the increase in the amounts of isotonic solution of sodium chloride in the preparation of the antigen suspensions. Efforts are being directed in this laboratory to standardize all Kahn antigens to exhibit sloping titers.

7. Kahn,[3] p. 53.

7. SUMMARY

A serologic method is presented, of a broader scope than current serodiagnostic tests, intended to supplement these tests in cases in which the diagnosis of syphilis is definitely established. This method, known as the optimal zone procedure, is based on the use of multiple serum: antigen ratios. By the use of these ratios, positive results may be obtained in known cases of syphilis in which serodiagnostic tests give negative results. Also, negative results given by the procedure following therapy in syphilis may serve as a better indicator of cure than negative results given by serodiagnostic tests. Finally, the method elicits different serologic patterns in different situations in syphilis—patterns which may indicate serologic trends of clinical significance.

Clinical material for this paper was furnished by Dr. Arthur C. Curtis, acting chairman of the department of dermatology and syphilology, University Hospital, University of Michigan; by Dr. Grant Morrow, of the same department; by Major Nelson Ryan, United States Public Health Service, director, Michigan Rapid Treatment Center, Ann Arbor, and by Dr. Loren W. Shaffer, director, Social Hygiene Clinic, Detroit. Technical assistance was rendered by Ella M. Brandon, Catherine Adams and Elizabeth B. McDermott.

Clinical Notes

MOLLUSCUM CONTAGIOSUM TREATED WITH SULFADIAZINE

CARL W. LAYMON, M.D., MINNEAPOLIS

In 1941 Sommerville [1] reported on 8 cases of molluscum contagiosum in which the patients had been treated with sulfapyridine. In 6 cases the disease cleared completely, and in 2 it was necessary to stop the treatment within a short time because of toxic reactions to the drug. Sommerville pointed out that sulfapyridine had a definite lethal effect on the causative virus of molluscum contagiosum. Four of Sommerville's patients who took sulfapyridine regularly in doses of 30 to 60 grains (2 to 4 Gm.) daily were cured within varying periods of two to eight weeks. For 2 patients who took the drug only at irregular intervals three to four months was required for complete cure. Two patients who failed to respond when the daily dose was 15 grains (1 Gm.) had clearing when the dosage was increased to 30 grains daily. Of the 6 patients who were cured, 5 were children ranging in age from 9 months to 15 years.

In 1942 Hill and Downing [2] reported another case of molluscum contagiosum in a white man aged 44, which responded favorably to sulfapyridine. There were fifteen lesions of one year's duration on the trunk and arms. The patient was given sulfapyridine (7½ grains [0.5 Gm.] four times daily), and within a week all the lesions except one had disappeared. The latter was removed by desiccation. There were no recurrences within four months following treatment.

A few months ago I observed a case of molluscum contagiosum in a child, in which the lesions were so numerous that local therapy would have been a formidable procedure. Chemotherapy with sulfadiazine was completely successful. The patient was a boy aged 12, who reported for examination on March 8, 1945. There were about a hundred lesions of molluscum contagiosum on the buttocks, in the intergluteal cleft and on the scrotum. Treatment with sulfadiazine (15 grains orally four times daily) was instituted on March 15. Within one week the lesions had diminished in size considerably. The dosage of the drug was reduced to 7½ grains four times daily, and within another week the only signs of the disease were pink macules at the sites of former nodules. There has been no recurrence in several months.

COMMENT

From the few reports in the literature it seems that both sulfapyridine and sulfadiazine are effective drugs in the treatment of molluscum contagiosum. Other sulfonamide compounds might be similarly useful. Because of possible toxic reactions the routine use of sulfonamide compounds in treating this disease, however, seems hardly justifiable, since simple harmless local measures are successful in ordinary cases. For certain persons, especially children, whose lesions are extremely numerous chemotherapy with sulfonamide compounds may be used.

From the Division of Dermatology, University of Minnesota, H. E. Michelson, M.D., Director.

1. Sommerville, J.: Molluscum Contagiosum and M. & B. 693, Brit. J. Dermat. **53**:255-257 (Aug.-Sept.) 1941.

2. Hill, W. R., and Downing, J. G.: Molluscum Contagiosum Cured with Sulfapyridine, Arch. Dermat. & Syph. **46**:139-140 (July) 1942.

PURPURA DUE TO IODIDES

Report of a Case

WILL C. DAVIS, M.D., and THOMAS S. SAUNDERS, M.D., PORTLAND, ORE.

The occurrence of purpuric manifestations following the administration of iodides was recorded in 1877 by Fournier.[1] Other reports were made by Robinson in 1893,[2] Milian in 1899,[3] Mackenzie in 1889,[4] Wilson in 1889,[5] Hudelo and Lebar in 1904 [6] and Dennig in 1933.[7] While cutaneous manifestations from the internal use of iodides are common, and, indeed, often anticipated, we feel that purpuric lesions are of sufficient rarity to justify this case report. We consider that purpura resulting from iodides is an ominous sign—if the use of the drug is continued, a fatality might result. Therefore one must recognize the possibility that purpura can be caused by the administration of iodides. In our experience, it occurs so rarely as to make one suspect other causes rather than the obvious (and true) one.

REPORT OF CASE

B. F., a 48 year old man, was first seen by one of us (W. C. D.) in November 1944. He complained of severe headaches, progressive loss of vision in the right eye and some unsteadiness of gait.

Physical examination showed a positive Romberg sign and diminished knee jerks and ankle jerks. The heart and lungs were normal.

Ophthalmologic examination showed 20/50 vision in the left eye and 20/200 vision in the right eye. The pupils were unequal and did not react to light. There was pallor of the optic nerves.

The Kolmer and Kahn serologic reactions of the blood were 4 plus. The Kahn reaction of the spinal fluid was 4 plus; there were 87 cells per cubic millimeter; the total protein level was 80 mg. per hundred cubic centimeters, and the colloidal gold curve (Lange test) was 011231000. Adiagnosis of tabes dorsalis (with primary atrophy of the optic nerve) was made.

On November 13 the patient was instructed to take 15 grains (1 Gm.) of potassium iodide three times daily. This was accompanied with weekly intramuscular injections of bismuth subsalicylate (0.2 Gm.). His headaches diminished in severity, and his vision rapidly improved. He reported some soreness in the salivary glands. This was attributed to the potassium iodide, but he was advised to continue taking it.

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1. Fournier, A.: Petechial Iodism, Rev. mens. de méd. et chir. **1**:653-664, 1877.
2. Robinson, T.: Rapid Production of Purpura After Small Doses of Iodide of Potassium, Lancet **1**:471, 1893.
3. Milian, G.: Iodide Purpura of the Buccal Mucosa, Presse méd. **2**:193, 1899.
4. Mackenzie, S.: Fatal Purpura From Iodide of Potassium, Illus. M. News **1**:169, 1888-1889.
5. Wilson, J. H.: Purpura Haemorrhagica from Iodide of Potassium, Brit. M. J. **1**:470, 1889.
6. Hudelo and Lebar: Purpuric Iodism with Probable Association of Tuberculides of the Angiokeratoma Variety, Bull. Soc. franç. de dermat. et syph. **15**: 361-364, 1904.
7. Dennig, H.: Thrombopenic Purpura Following Medication with Iodine, München. med. Wchnschr. **80**:562, 1933.

On December 1 definite purpura of the lower extremities was noticed by the patient and the physician. No other signs or symptoms were present. Examination of the blood at this time showed a hemoglobin content of 86 per cent (Sahli), 4,560,000 red cells, 12,400 white cells and 100,000 platelets.

Feeling that the bismuth was responsible for the purpura, we discontinued its use and administered oxophenarsine hydrochloride. However, the purpura persisted. Our attention was now drawn to the potassium iodide as a possible cause; hence

Purpuric lesions produced by readministration of potassium iodide.

it was discontinued. The purpuric lesions promptly disappeared. Since they cleared, we have been able to reproduce the lesion experimentally by a single dose of 5 grains (0.3 Gm.) of potassium iodide (fig.).

SUMMARY

A case of purpura from the administration of potassium iodide is reported. Because of its ominous import, we feel that the possibility of the production of purpura should be kept in mind whenever iodides are used.

Medical-Dental Building.
Medical Arts Building.

Abstracts from Current Literature

EDITED BY DR. HERBERT RATTNER

ACUTE SYPHILITIC MENINGITIS TREATED WITH PENICILLIN. RUSSELL A. NELSON and LEROY DUNCAN, Am. J. Syph., Gonor. & Ven. Dis. **29**:141 (March) 1945.

In 10 cases of acute syphilitic meningitis treated with penicillin intramuscularly, the immediate results were excellent, from both the clinical and the laboratory standpoint. While penicillin does not appear in the cerebrospinal fluid after frequent intramuscular administrations, the drug is effective against acute syphilitis meningitis when given by the intramuscular route.

Clinical relapse did not develop in any of the 10 patients treated (ninety-eight to three hundred and ten days after treatment). One patient showed a serologic relapse in the spinal fluid.

The total amount of penicillin administered to a patient varied from 600,000 to 4,000,000 units; the duration of treatment varied from seven and one-half to eleven days.

The authors recommend that patients with acute syphilitic meningitis receive a total of 2,000,000 to 3,000,000 Oxford units of penicillin administered by the intramuscular route every three to four hours day and night over a minimum period of eight to sixteen days.

FALSE POSITIVE SEROLOGIC REACTIONS FOR SYPHILIS WITH SPECIAL REFERENCE TO THOSE DUE TO SMALLPOX VACCINATIONS (VACCINIA). R. REIN and ELIZABETH S. ELSBERG, Am. J. Syph., Gonor. & Ven. Dis. **29**:303 (May) 1945.

Biologic false positive reactions occur with some frequency following vaccinations for smallpox, and it is important to rule out that possibility before antisyphilitic treatment is instituted. From the results obtained in this study it would seem that about ten to fourteen days must elapse after vaccination for smallpox before the first false positive reaction for syphilis is detected. A similar incubation period was noted in patients with primary atypical pneumonia, while in malaria false positive reactions are observed four to seven days after the first febrile attack.

Following vaccination the maximum degree of positivity was usually seen between the fourteenth and the twenty-first day. The majority of serums with false positive reactions due to smallpox vaccination became negative within three months.

PENICILLIN IN LATE SYPHILIS. J. H. STOKES and others, Am. J. Syph., Gonor. & Ven. Dis. **29**:313 (May) 1945.

The authors by means of tables and case records attempt to evaluate the status of penicillin in treatment of late syphilis. Striking improvements were obtained in syphilis of the central nervous system and in late cutaneous syphilis. Interstitial keratitis showed an erratic response to penicillin, and the response of serofastness in late latent syphilis is not encouraging thus far.

"As a general statement it may be said that penicillin, as the sodium salt of an as yet incompletely analyzed and understood substance, is an effective therapeutic agent in the treatment of late syphilis. Under conditions not yet clearly defined, it produces transformations, symptomatically and serologically, without reaction or even serious inconvenience to the patient, which are equal if not superior to those obtained by long and arduous procedures involving the arsenicals and heavy metals.

TIME-DOSE RELATIONSHIPS OF PENICILLIN THERAPY. W. MCDERMOTT, MARIA BENOIT and R. DUBOIS, Am. J. Syph., Gonor. & Ven. Dis. **29**:345, 1945.

Observations of the action of penicillin on infectious syphilis suggest that only short periods of action of penicillin are necessary for the immediate destruction of a large number of organisms but prolonged action is necessary for cure. In addition, there is some evidence that in vivo large increases in the concentration of penicillin for short periods do not shorten the period of time necessary for cure.

As both studies in vitro and clinical experience lend support to the thesis that it is not the production of multiple peaks of high concentrations of penicillin but the length of the action at low concentrations which is the important factor, it is suggested that the action time of penicillin be given consideration in the planning of new regimens for the treatment of syphilis.

There is a possibility that once the initial effect of the penicillin action has occurred subsequent action need not be absolutely continuous to obtain the maximum effect.

REUTER, Milwaukee.

TREATMENT OF SKIN DISEASES IN THE TROPICS. THOMAS W. CLARK, Bull. U. S. Army M. Dept., April 1945, no. 87, p. 70.

The cutaneous diseases most commonly encountered in an Army hospital served for more than a year and a half in the South and Southwest Pacific were dermatophytosis, dermatitis venenata and bites of insects and mites. The characteristics of these diseases were much the same as in temperate zones, but they tended to be more persistent and severer. Secondary infections complicated nearly every case, and most often it was the infection, and not the primary disease, that led to hospitalization.

Good general care, strict adherence to aseptic surgical technics and the judicious use of local therapy were the important factors in the treatment.

CONTACT POISON PLANTS IN THE OLD WORLD TROPICS. E. D. MERRILL, Bull. U. S. Army M. Dept., April 1945, no. 87, p. 115.

Many physicians perhaps do not realize that certain trees and some shrubs in the Old World tropics, all belonging in the same natural family of plants as the poison oak and poison ivy (Rhus), the Anacardiaceae, are violent contact irritants. Contact with the fresh sap, and some species with fresh leaves, or with freshly sawed lumber may cause violent dermatitis corresponding exactly to that caused by Rhus. The genus Rhus is of worldwide distribution and contains about two hundred described species, yet only a very few of the species are actually poisonous; these are confined to North America, eastern Asia and Japan. In the Indo-Malaysian region some of the species in certain other anacardiaceous genera are poisonous; all of these, with the exception of some shrubs of genus Semecarpus, are trees.

As in certain persons a characteristic eruption, known as mango rash, develops after the eating of the fruits of the common mango (Mangifera indica), it is suspected that the poisonous principle may be present in very small quantities in the fruit. It is also well known that the lumber of Gluta benghas, exported at times from Malaya to Europe and the United States, may cause severe dermatitis among the millmen and carpenters who work with it.

The treatment is the same as for Rhus dermatitis. The irritating principle being a nonvolatile, irritating oil, any use of salves should be avoided; such treatments merely tend to spread the irritating principle. Thorough washing or scrubbing with a warm, strong, alkali soap solution is always indicated; bathing in alcohol is also of value. Merrill states that one of the most effective methods of treatment is to bathe the affected parts with ordinary photographic hypo (saturated solution of sodium hyposulfite).

TRENCH FOOT: THE DIAGNOSTIC VALUE OF "ISCHEMIC PAIN." A. E. SCHECTER and CHARLES A. RAGAN, Bull. U. S. Army M. Dept., June 1945, no. 89, p. 98.

A type of pain brought on by vascular occlusion, which is seen almost exclusively in trench foot, is described. It is suggested that this pain is related to ischemia. It is believed that the severity of the local tissue damage in patients with trench foot can be correlated with the response to vascular occlusion. The procedure can be used to advantage in forward areas to determine accurately and promptly the diagnosis of trench foot. It is suggested that the term "ischemic pain" be applied to this phenomenon.

STRAKOSCH, Denver.

A FIELD STUDY OF LATENT TULAREMIA IN RODENTS WITH A LIST OF ALL KNOWN NATURALLY INFECTED VERTEBRATES. A. L. BURROUGHS, R. HOLDENRIED, D. S. LONGANECKER and K. F. MEYER, J. Infect. Dis. **76**:115 (March-April) 1945.

The authors found that latent tularemia infection was present in Rattus norvegicus, Microtus californicus and Peromyscus maniculatus. None of their ectoparasites were infected. The authors suggest the possibility of an air-borne transmission of tularemia among some rodents and include a list of vertebrates known to be naturally infected with tularemia.

CORNBLEET, Chicago.

DERMATITIS EXFOLIATIVA FOLLOWING ARSPHENAMINE THERAPY: OBSERVATIONS ON FIFTY CASES. M. J. COSTELLO and S. LANDY, New England J. Med. **232**:369, 1945.

Costello and Landy have observed 50 patients with exfoliative dermatitis attributable to arsphenamine, 26 women and 24 men, of whom 48 were improved or cured and 2 died. Forty-two had received neoarsphenamine; 2 had received oxophenarsine hydrochloride and 2 had received acetylglucoarsphenamine. Clinical jaundice occurred in 2 patients. Twenty-seven patients had a positive Wassermann reaction of the blood and 23 a negative one. Sodium thiosulfate administered to 30 patients proved of no value. Dextrose injected intravenously appeared to be of benefit. Crude liver extract administered intramuscularly had to be discontinued because of formation of abscesses. Recommendations for prevention and treatment are given.

AN EVALUATION OF SULFONAMIDE OINTMENT BASES. R. W. HOWARD, New England J. Med. **232**:698, 1945.

According to the experimental studies of Howard, if optimum therapeutic efficacy is to be realized all grease or cold cream bases for external applications of sulfonamide drugs should be avoided. Greasy bases obstruct the release of the drug. Moreover, they are not miscible with water; they are sticky and objectionable to the patients, and they are difficult to remove. High levels of sulfonamide compounds are released by oil in water emulsions, stearate vanishing creams, bentonite and pectin jelly bases.

A REVIEW OF RECENT FINDINGS IN FILARIASIS. D. R. A. WHARTON, New York State J. Med. **45**:500, 1945.

Because of the possibility of the introduction of filariasis into the United States with the return of the troops from the tropics, Wharton describes the various methods of diagnosing the disease—biopsy, finding of calcified worms by roentgenologic examination, presence of microfilarias in the blood and the cutaneous test. The treatment is symptomatic. Probably in many of the patients the infection will terminate spontaneously, and the menace to this country is relatively small.

MYCOSIS FUNGOIDES: TWO UNUSUAL TYPES, ONE PRESENTING LEONINE FACIES; THE OTHER, PARAPSORIASIS (?) IN PATCHES FOR THIRTY YEARS. E. W. ABRAMOWITZ and B. KANEE, New York State J. Med. **45**:512, 1945.

Two interesting cases of mycosis fungoides are described, one presenting a rare facial appearance resembling nodular leprosy and the other, presenting lesions of classic parapsoriasis for thirty years, later proved to be mycosis fungoides.

A BRIEF HISTORY OF DERMATOLOGY IN NEW YORK CITY: ITS SHARE IN THE PROGRESS OF THE SPECIALTY IN AMERICA. P. E. BECHET, New York State J. Med. **45**:629, 1945.

From the founding, in 1869, of the New York Dermatological Society, the oldest in the world, P. E. Bechet takes the reader through the beginning, in 1836, of American dermatology the opening by H. D. Bulkley of the Broome Street Infirmary for Diseases of the Skin, the appearance of the first journal on dermatology in 1870, the publication of Piffard's textbook on dermatology and the opening of the largest hospital for cutaneous diseases in America, the New York Skin and Cancer Hospital. Highlights of the lives of Bulkley, Piffard, Fox, Sherwell, Keyes, Robinson, Morrow, Fordyce, Pullitzer and Taylor are given.

RONCHESE, Providence, R. I.

NON-ACID-FAST FORMS OF THE MYCOBACTERIUM OF HUMAN LEPROSY. ELEANOR ALEXANDER-JACKSON, Science **101**:563 (June 1) 1945.

The author has developed a triple stain method which reveals non-acid-fast forms of Mycobacterium tuberculosis not disclosed by the usual Ziehl-Neelsen technic. With this method, acid-fast tubercle bacilli stain red; non-acid-fast forms (rods, granules and zooglea) stain blue, while other organisms, tissue cells, etc., form a light green background.

With this technic, nasal smears and smears from cutaneous lesions of patients with leprosy were studied. Of the 34 patients, 84 per cent showed zoogleic and granular or sporelike forms; 50 per cent showed zoogleic forms only; 40 per cent showed some acid-fast forms and 34 per cent showed acid-fast or non-acid-fast rod forms.

The author concludes that "while relatively few cases are reported here, and mycobacterium leprae cannot as yet be cultured on suitable media or successfully inoculated into animals in order to obtain absolute experimental proof, nevertheless, these findings strongly suggest that the mycobacterium of leprosy, like the mycobacterium of tuberculosis, has a zoogleal form or phase. The existence of non-acid-fast forms in leprosy may explain certain peculiarities in the course of the infection, such as its protracted incubation period, and the difficulty in demonstrating bacilli in certain types of lesions. The results of this limited study would seem to encourage more extensive observations with the aid of the Triple Stain Technic."

RATTNER, Chicago.

ERYTHEMA MULTIFORME. WERNER W. DUEMLING and THEODORE A. LESNEY, U. S. Nav. M. Bull. **44**:968 (May) 1945.

Ten cases of primary erythema multiforme are reported, all observed during the spring. In every case there was involvement of the oral mucosa, and differentiation from aphthous stomatitis, Vincent's angina, pemphigus and syphilis was required.

The average age of the patients was 22 years. The average temperature was 100 F., and the average duration of symptoms was 11.1 days. There was no particular racial distribution; all Kahn tests of the blood elicited negative reactions, and the cultures showed the usual saprophytic organisms.

FILARIASIS: HISTOPATHOLOGIC STUDY. PAUL MICHAEL, U. S. Nav. M. Bull. **45**:225 (Aug.) 1945.

On the basis of laboratory studies, the author concludes that filariasis should not constitute a public health problem in the continental United States and that instances of physical damage to the patient should be negligible. The immune reactions of the host together with the reticuloendothelial system are sufficient to destroy the parasite in most instances, provided the patients are evacuated from the endemic areas.

The presence of the parasite in the host initiates a characteristic foreign body granulomatous reaction. Many of the cutaneous manifestations seen in filariasis are presumed to be allergic in nature. For diagnostic purposes the laboratory method of choice is histologic examination of suspected lesions, for the examination of the blood for microfilarias is often inadequate.

The article includes eight excellent histopathologic illustrations in color.

RODIN, South Bend, Ind.

SCABIES PROPHYLAXIS WITH "TETMOSOL" SOAP. KENNETH MELLANBY, Brit. M. J. **1**:38 (Jan. 13) 1945.

Using a soap which contains 10 per cent Tetmosol (tetraethylthiuram monosulfide) Mellanby was able to control an epidemic of scabies in a mental disease hospital.

Eleven weeks after the onset of a heavy infestation most patients were cured and the spread of the disease was prevented.

PENICILLIN IN GONORRHOEA AND SYPHILIS. F. L. LYDON and W. R. SCOTT COWE, Brit. M. J. **1**:110 (Jan. 27) 1945.

The present dose of penicillin used in the treatment of gonorrhoea is approximately 100,000 units, a dose quite inadequate to cure syphilis but perfectly adequate to heal a primary lesion and influence, at least temporarily, the serologic reaction for syphilis.

The authors raise three theoretic questions without attempting answers at this time. 1. What interval must elapse before a positive Wassermann reaction or systemic manifestations of syphilis will develop in such an inadequately treated patient? 2. On the analogy that early syphilis inadequately treated with the arsenicals frequently exhibits precocious tertiary lesions, will this also hold true for early syphilis inadequately treated with penicillin? 3. On the same analogy, is not such a patient likely to remain infective during the assumed latent period?

IMPETIGO TREATED WITH SODIUM PENICILLIN CREAM. J. MUNRO GOLD, Brit. M. J. **1**:152 (Feb. 3) 1945.

The author succeeded in curing a patient with severe impetigo with a cream consisting of equal parts of hydrous wool fat, cod liver oil and water, to which was added enough sodium penicillin to make a cream of 500 Oxford units per gram.

SHAW, Chattanooga, Tenn.

INCIDENCE OF SCABIES IN A COMMUNITY USING ORDINARY SOAP AND TETMOSOL SOAP. W. BARTLEY, K. UNSWORTH and R. M. GORDON, Brit. M. J. **1**:332 (March 19) 1945.

The incidence of scabies in a closed community of 400 persons was observed over a period of thirty-one weeks, during the last thirteen of which Tetmosol soap was substituted for ordinary toilet soap.

During the eighteen weeks in which ordinary soap was used the incidence of scabies increased from 4 per cent to 9.2 per cent and 21 new cases were recorded. At the end of this period soap containing 5 per cent tetmosol (tetraethylthiuram monosulfide) was substituted for ordinary soap. During the remaining thirteen weeks of observation the incidence of scabies fell from 9.2 to 0.5 per cent and only 1 new case occurred. No cases of dermatitis were recorded.

SUBSTANCES USED FOR PEDICULOSIS CAPITIS. ELIZABETH SCOBBIE, Brit. M. J. **1**:409 (March 24) 1945.

D.D.T. emulsion and lethane hair oil are the two insecticides of outstanding value in the treatment of pediculosis. D.D.T. is preferable because one treatment properly carried out should produce cure in every case, and the odor is not unpleasant.

Since D.D.T. is insoluble in water, the hair can be washed without affecting its action. No toxic effect or irritation of the skin has been noted after the use of lethane hair oil or D.D.T. emulsion.

A CASE OF D.D.T. POISONING IN MAN. V. B. WIGGLESWORTH, Brit. M. J. **1**:517 (April 14) 1945.

The subject was a healthy laboratory worker who was attempting to determine whether D.D.T. (dichlorodiphenyltrichloroethane) was liable to cause any local irritation. He deliberately allowed small quantities of acetone solution of D.D.T. to evaporate on the back of his hand and further permitted the hands to be immersed in a solution of D.D.T. for several minutes. Within the day symptoms developed, consisting of a feeling of heaviness and aching in the extremities and weakness in the legs. Symptoms became progressively worse until sleep became almost impossible because of periods of extreme nervous tension and involuntary muscular tremors. The subject had not recovered at the end of ten weeks. The case recorded is one of deliberate exposure to amounts of D.D.T. far in excess of any that would be likely to be encountered in practice.

HYPERTRICHOSIS WITH MENTAL CHANGES: EFFECT OF ADRENALECTOMY. RAYMOND GREENE, A. SPENCER PATERSON and G. C. L. PILE, Brit. M. J. **1**:698 (May 19) 1945.

A case of hypertrichosis associated with mental changes which gradually resolved after adrenalectomy is reported. Within two months after operation there was no sign of further growth of hair.

TREATMENT OF IMPETIGO. MARY S. SMITH and E. COLIN JONES, Brit. M. J. **1**:699 (May 19) 1945.

The authors feel that antiseptics are not necessary in the successful treatment of impetigo. They recommend a method of treatment with simple calamine liniment which depends on the following six principles: first, exposure of all parts to treatment—by shaving if necessary; second, avoidance of trauma; third, insuring that the dressings are kept in close contact with the affected parts and that they remain moist; fourth, removal of dressings for only the few minutes necessary for shaving or redressing and immediate reapplication; fifth, inclusion of all outlying lesions in the treatment with the dressing extending about 1 inch (2.5 cm.) beyond the borders and sixth, alteration in the method of applying the medicament as occasion demands—e. g., from compresses to smears—with no alteration in the remedy itself.

SHAW, Chattanooga, Tenn.

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILIS

Harry C. Saunders, M.D., *Chairman*

Frank Vero, M.D., *Secretary*

Dec. 5, 1944

Pemphigus Vegetans. Presented by DR. TIMOTHY J. RIORDAN.

T. C., a woman aged 52, was admitted to Bellevue Hospital on July 18, 1944. About eight months prior to admission "blisters" developed on the lips, roof of the mouth, tongue and buccal mucosa. For six months the lesions were confined to these areas. About two months before admission new lesions developed on the scalp and in the axillas, groin and intermammary folds. Examination of the skin showed bullae varying from a few millimeters to 1.5 cm. in diameter on the forehead, commissures of the mouth, upper lip, chin, axillas and groin. In the mouth there were bullae and ulcerations involving the palate, tongue and buccal mucosa.

About six to seven weeks after the patient was admitted to the hospital several discrete, moist vegetative lesions developed in the axillas, in the groin and in the left intermammary area. These lesions gradually developed a flat, smooth surface, erythematous in appearance. Under continued treatment, the lesions regressed, leaving pigmented areas.

Laboratory studies showed the urine to be normal, and the Wassermann reaction of the blood negative; a blood count showed 12,250 leukocytes, with 71 per cent polymorphonuclear leukocytes, 15 per cent lymphocytes, 8 per cent monocytes and 6 per cent eosinophils.

The patient was given carbarsone tablets. Beginning with 0.25 Gm. a day, the dose was increased to 0.75 Gm. daily. The total amount given was 16 Gm.

DISCUSSION

DR. E. WILLIAM ABRAMOWITZ: The bullous and vegetating lesions lasted about eight or ten months, rather an accelerated pace for a benign pemphigus. The patient is apparently in good health now and was not extremely sick during the entire time. Judging from the pigmentation and the configuration now present, I think that there is a possibility that the eruption is of the erythema multiforme fixed type, possibly resulting from a drug. The patient is entirely too insistent on the fact that she takes no drugs. There are few persons who do not take some medicines at one time or another.

DR. FRANK C. COMBES: This case is an interesting one from several standpoints. Ordinary pemphigus vulgaris—and by that the bullous type is usually meant—is characterized by alternating periods of exacerbation and remission. Many patients will get over their first siege without a great deal of difficulty, no matter what medicine is used. The second exacerbation will be stormier, and during the third it does not matter greatly what therapy is used. Pemphigus foliaceus and pemphigus vegetans are both usually gradually progressive, without remission. This case I have watched for some time. The patient had all the earmarks of pemphigus, if there are such things, with bullae particularly in the mouth and around the lips and hypoproteinemia with inversion of the albumin-globulin ratio, on which much importance is placed. This patient had tremendous vegetative lesions in the axillas, and there is no doubt in my mind that the diagnosis is pemphigus.

DR. LOUIS TULIPAN: I also observed this case for a long time, and I feel that the diagnosis was correct. Am I to understand that Dr. Abramowitz means that if a case runs on for ten months with benign symptoms the diagnosis should be changed?

DR. TIMOTHY J. RIORDAN: I am grateful for the discussion of this case. I should like to mention that one of my reasons for presenting the case is to show the favorable response to a pentavalent arsenical, carbarsone (4-carbamidophenylarsonic acid) given at Bellevue Hospital at the suggestion of Dr. Robert P. Little, who is now preparing a preliminary report on these cases.

Pernio with Milia. Presented by DR. TIMOTHY J. RIORDAN.

M. L., a man aged 47, is presented from St. Vincent's Hospital, with an eruption of the ear lobes of ten months' duration. The patient has worked in a butcher plant for twenty years, spending eight to ten hours daily in the refrigerator at a temperature of 14 to 34 F. Ten months ago he noticed itching, burning and swelling of the lobes of the ears.

Examination shows a heavy-set man with flushed face and cyanotic skin and ears. The ear lobes are tumefied and red and are studded with numerous pinhead-sized yellow milia which on acupuncture yield sebaceous, cheesy material. There are numerous lanugo hairs.

Laboratory examination showed that the urine was normal. The blood count showed: hemoglobin, 100 per cent; red blood cells, 5,100,000, and white blood cells, 5,000, with 60 per cent polymorphonuclear leukocytes, 36 per cent lymphocytes and 4 per cent monocytes. The tuberculin test elicited a strongly positive reaction in a dilution of 1:100,000. Guinea pig inoculation gave negative results, even after prolonged observation. Roentgenologic examination of the chest showed the heart to measure 17 cm. in its transverse axis, which is slightly over average normal measurement. The aorta was moderately dilated. There was congestion in the central zones and bases of the lungs but no evidence of recent parenchymal infiltration or pleural involvement. There is billowing of both sides of the diaphragm.

Biopsy showed the epidermis to be extremely thin. In the corium were found small epidermoid cysts filled with keratin. Between the cysts, the corium was densely infiltrated with lymphocytes and larger reticuloendothelial cells.

DISCUSSION

DR. MAX SCHEER: The diagnosis of pernio, I think, is correct. The presence of milia is an unusual feature. I do not recall having seen it before in pernio.

DR. JACK WOLF: I think that Dr. Scheer's remarks are well taken. This is a favored site for small sebaceous cysts, and I think that is a more likely diagnosis than milia. I also noticed comedo-like lesions.

DR. TIMOTHY J. RIORDAN: In connection with Dr. Wolf's remarks about sebaceous cysts, these lesions were true milia and not at all like the steatomas I noted at first. I found that it was difficult to remove the milia. They were keratin balls and not sebaceous material, as mentioned in the report. Incidentally, in that particular area I found a practical method of removing the milia: I used a mouse tooth forceps, clamped the milium and broke the skin at the base, and it shelled out readily.

I thought that some of these lesions bore a resemblance to tuberculosis, and the case was carefully studied, with roentgenologic examination of the chest and inoculations of a guinea pig. After two or three months the results of the latter were negative and the Mantoux test was strongly positive. The response to the removal of milia was striking. Of course, the man was warned about exposure to cold by going into the refrigerator in the course of his work.

Lichen Sclerosus et Atrophicus (Hallopeau). Presented by DR. TIMOTHY J. RIORDAN.

C. N., a white woman, is presented from St. Vincent's Hospital, with an eruption on the neck and chest of fifteen months' duration. There are four alabaster white, hidebound patches up to 2 inches by ¾ inch (5 by 1.9 cm.) in diameter above and below the clavicle and the sides of the neck and chest, with a 2 mm. pink areola, and several pinhead-sized white satellite atrophic lesions.

The Wassermann reaction of the blood was negative; the urine was normal and the blood count showed 90 per cent hemoglobin, 4,950,000 red blood cells and 9,500 white blood cells, with 76 per cent polymorphonuclear leukocytes and 24 per cent lymphocytes.

Biopsy showed the epidermis to be atrophic. In one area there was a piling-up of atrophic-looking prickle cells. In the corium there was a mild round cell infiltration. The granular layer was beaded, and in the subepidermal spaces there were casual areas of cellular elements pushed close to the epidermis, suggesting lichen planus.

DISCUSSION

DR. FRANK C. COMBES: This case had all the clinical characteristics of the disease as presented. I think that the eruption is a perfect example of this dermatosis and agree with the original diagnosis.

DR. MAX SCHEER: This patient also presented in some lesions the horny plugs which are found in this disease, at least in the early stage. Later, I understand, these plugs fall out and disappear.

A Case for Diagnosis (Boeck's Sarcoid?). Presented by DR. TIMOTHY J. RIORDAN.

M. S., a white woman aged 55, is presented from St. Vincent's Hospital, with a lesion on the left side of the nose, of eight months' duration.

Examination discloses a small cherry-sized, nonpainful, erythematous, infiltrated patch on the left side of the nose in the region of the lacrimal sac. There is no history of injury or disease of the eye.

The Wassermann reaction of the blood was negative, and the urine was essentially normal. Roentgenologic examination after injection of iodized poppyseed oil into the left lacrimal sac revealed normal conditions. Roentgenologic examination of the paranasal sinuses showed the frontal sinuses to be of average size, without pathologic changes. The ethmoid sinuses showed chronic involvement on both sides. The antrums were asymmetric, the right being smaller. Some mucosal thickening was seen in the floor and lateral wall of the right antrum. The sphenoid sinuses showed nothing unusual.

Biopsy showed a tiny bit of white tissue which consisted of corium containing many sebaceous and sweat glands.

DISCUSSION

DR. EUGENE TRAUGOTT BERNSTEIN: I agree with Dr. Rosen that one is dealing here with Boeck's sarcoid. It is a question whether the related conditions of Boeck's sarcoid, Darier's sarcoid, lupus pernio, erythema induratum, tuberculosis nodularis of the hypodermis, benign lymphogranulomatosis, osteitis tuberculosa multiplex cystoides and similar disorders should not be plainly named sarcoidosis. I should like to ask whether these diseases should continue to have different names, or should all these entities be placed under the term sarcoidosis?

DR. MAURICE J. COSTELLO: I agree with the diagnosis.

DR. CHARLES WOLF: I believe that this solitary lesion has some features which one may consider as possibly of a malignant nature. The patient has seborrheic dermatitis, which is incidental. The inner canthus of the eye is a favorite site for epithelioma, and the patient is at the age when epithelioma is more apt to develop. Sarcoid or sarcoidosis is a disease of early or middle life. I therefore suggest another biopsy.

DR. FRANK C. COMBES: I do not think that the diagnosis of sarcoid should be accepted too quickly in this case. It is a possibility, but I do not think that there is enough evidence at present to justify it. There are no clinical systemic characteristics of sarcoid. On further investigation this may prove to be a case of that disease, but it appeared to me that one may be dealing with a type of scrofuloderma or some other type of tuberculosis. There is, however, no history of tuberculosis in the family. I believe that the patient should have a complete study, including tuberculin tests. Anergy would point toward sarcoid and hyperergy to scrofuloderma.

DR. MAURICE J. COSTELLO: I agree with the diagnosis as presented, but I thought on palpating the lesion that it was a little softer than one would expect to find in sarcoid. This is the most common location for a single lesion of sarcoid. I think that a favorable response to roentgen rays would be in favor of sarcoid and against lupus erythematosus. Tuberculin studies should be carried out.

DR. ISADORE ROSEN: This condition should be recognized by the microscopic examination. It is difficult for one to make a diagnosis from the clinical features alone, because sarcoids may vary in appearance from that of granuloma annulare to that of lupus tumidus. Age does not play an important role in differential diagnosis.

DR. TIMOTHY J. RIORDAN: As to the remarks of one speaker about lupus erythematosus, at no time during the course of this lesion was there any evidence of scaling. It remained the same, with a shiny surface. I agree that a biopsy is important in establishing a diagnosis in this case. I think that Dr. Combes' suggestion of the possibility of the scrofuloderma type of tuberculosis is good. In the case of a shiny lesion without any definite nodular border or waxy appearance, I thought that I could rule out epithelioma, though not entirely. As a matter of fact, when I first saw the patient, the differential diagnosis was between sarcoid and epithelioma.

Secondary Syphilis: Condyloma Latum in the Nostrils. Presented by DR. GIRSCH D. ASTRACHAN.

A. D. S., a man aged 46, born in Italy, registered at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Nov. 9, 1944, with the history of an eruption in the nostrils of a few weeks' duration. The patient noticed some difficulty in breathing through his nose; he found a small pimple in the right nostril which had greatly increased in size by the following week. At that time the same kind of lesion appeared in the left nostril. The patient also recollected having had a slight swelling of the penis about four months ago.

Examination disclosed in both nostrils, attached to the lateral aspects, dime-sized to nickel-sized, elevated, dark gray, button-like, somewhat indurated, partly verrucous and partly smooth lesions. These obliterated the larger part of the orifice of the nostrils. The patient also presented around the anal region three pea-sized to bean-sized, well defined, elevated, indurated, round, flat, papular lesions, covered with a gray membrane. A dark field examination of the serum from one of the perianal lesions showed the presence of Treponema pallidum.

The patient was treated with penicillin and dichlorophenarsine hydrochloride from November 22 to November 24, receiving a total of 1,800,000 units of penicillin and 375 mg. of dichlorophenarsine hydrochloride. The lesions in the nostrils and around the anus showed a definite improvement.

Examination on Dec. 2, 1944 showed on the lateral aspect of both nostrils several flat, dark gray, pea-sized, elevated, soft, closely set lesions with rough surfaces. Around the anus are seen three small, pea-sized, elevated, gray papular lesions.

The serologic reaction of the blood was positive on two occasions (November 16 and 28). The complete blood count was normal except for a slight anemia (red blood cells 4,200,000) and leukocytosis (white blood cells 12,100). On November 24, after two days of therapy with penicillin, the blood count was normal. The leuko-

cyte count decreased to 10,500. The urine was normal. The icterus index was 9.4 on November 25.

Histologic examination by Dr. Charles Sims confirmed the diagnosis of secondary syphilis.

DISCUSSION

DR. GIRSCH D. ASTRACHAN: I presented this case because of the unusual location of the condylomas. I have never seen a case of this kind, nor have some of my associates with whom I discussed the problem. Another interesting feature in this case is the change in the blood count following two days of penicillin therapy. The number of red blood cells increased from 4,200,000 to 5,250,000, and the white blood cells decreased from 12,100 to 10,550.

Atopic Eczema (Allergic Eczema). Presented by DR. H. VICTOR MENDELSOHN.

M. W., a woman aged 32, was admitted to Bellevue Hospital on Oct. 10, 1944. The history disclosed that the patient had eczema in childhood, up to the age of 7 years. From the age of 7 to 13 she was free of cutaneous eruption. At the age of 13 she had a recurrence of the eczema, with remissions and exacerbations up to the age of 26, when her second child was born. From that time on, the patient has not been entirely free from cutaneous lesions. In addition, recurrent attacks of asthma began to develop, the last attack occurring about three months ago. The present dermatologic exacerbation began during the summer, with dryness, roughening and a tendency toward cracking of the skin of the legs, thighs and abdomen. Later her face, neck, arms and hands became involved, and finally the skin of the entire body was affected. At times the skin would be so dry that there was considerable scale formation. Two years ago the patient underwent scratch tests at the Long Island College Clinic and reacted positively to many foods. Avoidance of these foods has had no effect on the eruption.

Examination of the skin showed a generalized dermatitis, which was especially pronounced on the face, neck, chest, extremities and genital area, characterized by an erythematous, lichenified, dry, leathery surface, with many adherent, moderately thick scales and crusts. There were moist areas on the upper lips as well as on both postauricular regions and the posterior surface of the neck. On the back and abdomen there were many papules, yellowish white in appearance and 3 to 6 mm. in diameter, some with hemorrhagic centers. The left genitocrural area showed erythema.

The urine was normal. The white blood cell count showed 19,000 leukocytes, with polymorphonuclears 45 per cent, lymphocytes 27 per cent, eosinophils 21 per cent, monocytes 4 per cent, transitional cells 2 per cent and basophils 1 per cent. The Wassermann reaction of the blood was negative.

Treatment consisted of (1) fever therapy, by the administration of gradually increasing doses of typhoid vaccine intravenously; (2) ultraviolet irradiation therapy; (3) aolan (sterile solution of lactalbumin in colloidal form) intramuscularly, and (4) topical applications.

The patient has shown definite improvement during hospitalization. The extreme dryness and roughness of the skin have diminished; the moist areas have disappeared, and the pruritus is much less.

DISCUSSION

DR. E. WILLIAM ABRAMOWITZ: The treatment of such patients is unsatisfactory from every standpoint. The determination of the allergic status is usually not of much help. Every one has seen patients who have had this disease from childhood. Sometimes it disappears after several years, and sometimes it lasts until the age of 30 or 40. The improvement in this case with fever therapy is only temporary. I think that the emotional element is of importance, because emotional upsets will bring about a recurrence. This is the type of disease which comes under the classification of psychosomatic disorders. When patients are removed from their usual

environment, they improve greatly. The crusted excoriations on the skin of the arms are like neurotic excoriations, but the lichenification present indicates what is called atopic dermatitis.

DR. ABRAHAM WALZER: I should like to discuss two aspects of this question. First, the name. The original conception of this disease was given by the French school (Vidal, Brocq and Besnier—especially the last), and they described the entity as neurodermatitis. If one takes their description and conception of this disease and compares them with the present conception of atopic eczema, it will be noted that the two are practically the same. If the term "allergy" is substituted for their "diathesis," one gets the present conception of neurodermatitis.

Second, the allergic aspect. By labeling this condition atopic eczema, I think that Dr. Mendelsohn should have made an attempt to connect it with allergy. There is a definite family history of asthma, and the patient also suffers from it. This woman therefore, has atopy. Direct testing of these patients is of no value. The skin of persons with neurodermatitis will often give false reactions. Indirect testing must be employed.

In treatment, elimination of offending allergens is not the only thing to be done. These patients have scratched for years and have produced a dermatitis which is more or less fixed. With local treatment and elimination of allergens, 75 per cent benefit can be obtained. These patients, however, will often improve temporarily with almost any treatment or with none. In other words, remissions and relapses are common in the course of the disease. The improvement following the injection of typhoid vaccine or psychotherapy, therefore, just represents the natural course of the disease and not the value of this specific therapy.

DR. EUGENE TRAUGOTT BERNSTEIN: I do not intend to harp on the subject of psychosomatic cutaneous disorders. The skin is the mirror of the soul; one really does not know how imponderable psychic influences may affect the physical being to the extent that the person may drop dead. The skin as an expressive organ reflects emotional states from within and responds to psychic insults from without. The psychologic aspect plays an important part in the treatment of disorders of the skin. It is known that when a patient is given a new therapy, be it an injection of vitamin B, a salve, the reassurance of a new physician or other psychologic influences, the skin may improve dramatically in a short time; then, as the patient stays with the physician for a time, there is an exacerbation of the original condition. There is no doubt that a strong connection exists between psychic influences, emotional upsets, unpleasant environment and the states of acuity or amelioration of the cutaneous disorder. In cases of dermatologic disorders with a psychologic aspect, the patient should be subjected to neuropsychiatric treatment. I think that the present restless time is responsible for the "no man's land" where dermatology and psychiatry meet. Each of these specialties has its boundaries, beyond which it is unwise to transgress, but the cooperation between dermatologists and psychiatrists should prove mutually constructive and profitable.

DR. H. VICTOR MENDELSOHN: This case was presented not for the purpose of demonstrating a new or specific type of treatment in cases of atopic eczema generally but rather to show that in this instance improvement was largely due to this form of therapy and was not the result of change of environment alone. I was glad to hear Dr. Abramowitz call attention to the emotional factors in the causation of these eruptions. In my opinion, the importance of this fact cannot be overemphasized. Treatment in most if not in all cases of atopic eczema should include the correction of neurogenic and emotional disturbances.

Dr. Walzer raised a number of interesting questions which I should like to discuss at great length, but the lateness of the hour permits only brief references. I thoroughly agree with him that this patient should not be tested by the scratch or intradermal method, with her skin in the present condition. Such patients, however, can receive these tests during periods of remission, when they present ample areas of normal skin. The indirect method of testing has many advantages over the direct methods. The former, besides permitting the testing of patients

who present no healthy skin, also enables the demonstration of specific antibodies for certain allergens in the patients' serum. Nevertheless, even with this method of testing, the actual demonstration of causative agents in atopic eczema and other dermatoses has not been successful in my hands.

In 1934 I reported an allergic study of 262 cases of various dermatoses, including 86 cases of eczema, most of which were atopic eczema (Sensitization Tests: Their Value in Dermatology, ARCH. DERMAT. & SYPH. **29**:845 [June] 1934). Direct, indirect and patch tests were performed. This study was carefully carried out; some of the patients were observed over a period of three to four years. Collectively, the patients with atopic eczema gave a large number of positive reactions, but the ingestion or avoidance of the positively reacting substances had little or no effect on the disease. The cause was demonstrated in 1 case and partially demonstrated in 8 others. Atopic eczema is indeed a complex problem, the causation and the therapy of which are still uncertain.

I agree with Dr. Walzer that the terms flexural eczema, neurodermatitis, neurodermite, neurodermatitis disseminata, atopic eczema and atopic dermatitis are not clear in the minds of many dermatologists. May I add to this list the terms eczema and dermatitis? In reading reports dealing with eczematous eruptions, one frequently does not know what the writer had in mind. The disease entity which this patient presents is designated by the official nomenclature as atopic eczema (neurodermatitis disseminata).

HAWAII DERMATOLOGICAL SOCIETY

James T. Wayson, M.D., *President*

Harry L. Arnold Jr., M.D., *Secretary*

Dec. 9, 1944

A Case for Diagnosis (Pityriasis-Rosea-like, Lichen-Planus-like Eruption Following Antisyphilitic Therapy?) Presented by DR. HAROLD M. JOHNSON.

A 34 year old Filipino had been treated for syphilis since May 31, 1944. He received a course of bismuth and a course of arsenic (oxophenarsine hydrochloride), and when bismuth was started again, on Sept. 20, 1944, a pruritic scaly exanthem with discrete scaly macules and papules following the lines of cleavage developed on his chest, arms and legs. The lesions are definitely pityriasis-rosea-like, with the dusky purplish hue of lichen planus. The patient complained of severe itching in periodic seizures. Antisyphilitic therapy was discontinued, and a plantation physician gave the patient sodium thiosulfate and calcium gluconate intravenously and antipruritic lotions.

He was seen on Dec. 4, 1944, and a specimen for biopsy was taken from a typical scaly purplish papule located on his abdomen. The blood and urine were normal.

Biopsy showed hyperkeratosis of the horny layer, prickle cell metaplasia of the basal layer, with sharp-pointed rete pegs, a dense lymphocytic infiltrate in the corium, tightly packed against the epidermis, and abundant chromatophores. It was regarded as characteristic of lichen planus.

DISCUSSION

DR. HARRY L. ARNOLD JR.: I thought that this patient had annular atrophic lichen planus.

CAPT. HERBERT LAWRENCE, M.C., A. U. S.: In Los Angeles, about five years ago, there was much interest in eruptions following the administration of bismuth, which had not been observed previously. Clinically, this case is identical with some of the cases that were seen there at that time.

DR. HARRY L. ARNOLD JR.: By "identical" do you mean that the lesions were elevated, infiltrated annules with depressed hyperpigmented centers like those of this man? The eruptions of this sort that I recall seeing at meetings of the Detroit Dermatological Society at about that time were almost all pityriasis-rosea-like eruptions, chiefly in Negroes, in which hypopigmentation was the principal feature of the lesions

CAPT. HERBERT LAWRENCE, M.C., A. U. S.: There are two distinct morphologic pictures: a pityriasis-rosea-like eruption without hyperpigmentation and a lichen-planus-like eruption with hyperpigmentation. Rarely both eruptions would appear in 1 patient.

DR. HAROLD M. JOHNSON: I have seen pityriasis rosea following the administration of both bismuth and arsenic, but this is the first time I have seen lichen planus following the administration of bismuth.

CAPT. HERBERT LAWRENCE, M.C., A. U. S.: At the time of which I speak, it was noted that since lichen planus usually responded well to injections of bismuth it was odd that the eruption should follow the administration of bismuth. However, I have seen a patient with lichen planus who became much worse and in whom bullous lesions developed after the administration of bismuth.

DR. HAROLD M. JOHNSON: I have started this man on intramuscular injections of bichloride of mercury three times a week, and I also gave him an injection of mercuric salicylarsonate this morning.

CAPT. HERBERT LAWRENCE, M.C., A. U. S.: It is of particular interest that this eruption followed not the initial administration but the readministration of bismuth after a period during which no bismuth was given. This suggests a latent period, during which sensitivity developed.

CAPT. IRVING N. HOLTZMAN, M. C., A. U. S. (by invitation): I think that it is lichen planus. It may be due to bismuth.

CAPT. L. H. ROSENTHAL, M. C., A. U. S.: I agree with the diagnosis. Lichen planus may have multiple causes, and it may be produced by injections of almost any of the heavy metals.

Lichen Nitidus. Presented by DR. HAROLD M. JOHNSON.

A 7 year old Chinese schoolboy gave a history of a generalized eruption which had begun in January 1944. The lesions began on his abdomen and gradually spread to cover his entire body except palms, soles, scalp and lips. The patient was not ill and had no subjective symptoms. In June 1944 the rash disappeared after an attack of measles, but it returned one month later. The father had a history of tuberculosis; the child's past history was otherwise essentially noncontributory.

The patient presents a profuse generalized eruption of flat-topped, pinhead-sized, flesh-colored papules, which do not coalesce. The lesions are so close that they present a nutmeg grater appearance in some areas. There are several areas where Koebner's phenomenon is well shown, the papules being arranged in fine linear streaks. The genitalia are covered with the minute millet seed papules. The hard palate has a small papular patch.

The blood was normal with the exception of eosinophilia of 3 per cent. A roentgenogram of the chest was noncontributory. The Mantoux test elicited a negative reaction.

Treatment has consisted of the administration of vitamin A, 150,000 units daily, and weekly injections of bismuth subsalicylate (40 mg.).

The biopsy showed a sharply outlined infiltrate of epithelioid cells and lymphocytes situated in the papillary layer of the corium, with the epidermis displaced abruptly upward over it.

Lichen Scrofulosus (Tuberculosis Lichenoides). Presented by DR. HARRY L. ARNOLD JR.

A 12 year old part-Hawaiian boy was presented a year ago with a diagnosis of lichen scrofulosus, which was not confirmed by biopsy, and with only a weakly positive reaction of the skin to 0.005 mg. of purified protein derivative of tuberculin.

Under treatment with cod liver oil orally, the eruption slowly increased in extent and severity until February 1944, when, after a mild sunburn, the whole eruption subsided completely. In November the patient experienced a relapse, and he now presents about the same appearance as before. The clinical resemblance to lichen nitidus is somewhat more striking now than at the time of his last presentation.

DISCUSSION OF THE TWO PRECEDING CASES

DR. HAROLD M. JOHNSON: I should like to point out that the typical histologic changes of lichen nitidus were found only after repeated sections had been cut from the biopsy specimen. Ellis and Hill have suggested that lichen nitidus is a variant of lichen planus, and on that basis I have treated this boy with bismuth. It is interesting that the eruption cleared completely after an attack of measles in June but that the patient had a recurrence.

CAPT. DAVID MUSMAN, M. C., A. U. S.: Why do you not give him human measles immune globulin?

DR. HARRY L. ARNOLD JR.: In regard to the boy presented as having lichen scrofulosus, I must admit that neither the histologic changes nor the weakly positive reaction to purified protein derivative of tuberculin is particularly consistent with the diagnosis. I recently noted that the illustrations of the histologic changes of lichen scrofulosus in Sutton's text are as good pictures of lichen nitidus as those given under the heading of lichen nitidus, or perhaps even better.

CAPT. L. H. ROSENTHAL, M. C., A. U. S.: Pinkus, in his original description of lichen nitidus, classified it as a tuberculid.

DR. HARRY L. ARNOLD JR.: Does any one have any suggestions for the treatment of the boy with the lichen scrofulosus?

DR. HAROLD M. JOHNSON: Is it lichen scrofulosus?

CAPT. IRVING N. HOLTZMAN, M. C., A. U. S. (by invitation): Clinically, it certainly looks like it.

DR. HAROLD M. JOHNSON: I should suggest the administration of vitamin A, 300,000 to 500,000 units daily. It looks to me as if it might be phrynoderma.

Subacute Disseminated Lupus Erythematosus. Presented by DR. HARRY L. ARNOLD JR.

A 23 year old white housewife, previously presented before this group with a disease shown as an example of subacute disseminated lupus erythematosus, is presented again to show (1) the failure of 200,000 units of penicillin given intramuscularly in forty-eight hours to affect her condition; (2) the persistence of hypocholesterolemia, at a level of 57 mg. per hundred cubic centimeters in September and 69 mg. now, despite a basal metabolic rate only 14 per cent above normal, and (3) the effect of strong solution of iodine U. S. P., 5 drops twice daily. Since she has taken strong solution of iodine (seven weeks) she has felt better and has gained weight; the white blood cell count has dropped from 6,000 to 4,000 and from 77 to 67 per cent polymorphonuclear leukocytes; the erythema multiforme has become somewhat severer and more extensive; there was a period of nearly three weeks during which she was uncomfortable as the result of a diaphragmatic pleurisy on the left; the sedimentation rate has remained close to 60 per cent, and the Weltmann coagulation band has remained at 8. The urine still shows no abnormality.

The patient is also presented for suggestions as to treatment and for opinions as to the advisability of trying penicillin again in a more nearly adequate dosage.

DISCUSSION

DR. HARRY L. ARNOLD JR.: Dr. Herman Beerman recently told me that a patient with this disease treated with penicillin some months ago in Philadelphia is still getting along well. However, it is listed as one of the diseases in which the administration of penicillin is useless. I think that every one would agree that the trial of penicillin previously made in this case was inadequate because of the small dose. I think that a larger amount of the drug can be obtained for her now.

It was the consensus of the members that penicillin was worth trying again in more nearly adequate dosage.

NOTE.—Penicillin, in a total dose of 2,000,000 units in eight days, had no beneficial effect whatever.

Epidermolysis Bullosa. Presented by DR. HAROLD M. JOHNSON.

A 7 month old Japanese girl was first seen on Sept. 22, 1944. There was a history of chronic, crusted, impetiginous lesions on the dorsa of the feet, hands, knees and elbows since birth. Dime-sized to quarter-sized bullous lesions would appear on the plantar surface of the feet and heels after moderate trauma.

An uncle had the same type of dermatosis at birth, but it gradually disappeared.

Physical examination shows a well developed baby with many old healed scars on the plantar surface of the feet and heels. There are several bullous lesions on the dorsa of her hands. There is a suggestion of early epidermal denudement on the vulva. The mucous membranes of the mouth and the nails are not involved.

DISCUSSION

The members agreed with the diagnosis as presented.

Dermatitis Herpetiformis. Presented by DR. HAROLD M. JOHNSON.

A 13 year old Chinese boy was first seen on Nov. 15, 1944, with a history of an extremely pruritic dermatitis of his legs, buttocks, shoulders and arms, which had been present for five years. The family history and the past history are irrelevant.

Examination reveals an excoriated vesicular-papular rash in symmetric grouped arrangement. There is pigmentation and scarring of old, healed lesions. Mild secondary infection was noted in some patches after they had been scratched.

The course of the disease had been variable. There were many periods of quiescence followed by episodes of extreme pruritus. The patient has seen several physicians, with considerable relief in some instances. He previously received sulfathiazole and sulfapyridine by mouth, with moderate but incomplete relief.

A hemogram on Dec. 8, 1944 showed a hemoglobin content of 71 per cent, red cells 4,390,000, white cells 8,400, polymorphonuclear leukocytes 48 per cent, lymphocytes 45 per cent, eosinophils 4 per cent and monocytes 3 per cent. There had previously been a 28 per cent eosinophilia in the vesicle fluid.

An intramuscular injection of bismarsen, 0.1 Gm., was followed by relief of itching within a few days. The administration of the drug is being continued.

DISCUSSION

DR. HARRY L. ARNOLD JR.: The response to bismarsen is interesting if it is not just another spontaneous remission.

Dermatitis Herpetiformis. Presented by DR. HAROLD M. JOHNSON.

A 27 year old white woman came to the office on Dec. 8, 1944, with a history of a severely pruritic dermatitis of the back, chest and thighs since the age of 13. The lesions have been papular, with occasional vesicles which appear in crops. The lesions and pruritus disappeared several years ago, after a mild illness producing a temperature of 103 F., but promptly returned in a few days, after the convalescence. The patient has been seen by many dermatologists on the mainland and has received as many diagnoses.

The patient is a highstrung, underweight woman whose entire back is covered with excoriated papules. There are extensive hyperpigmentation and scarring, showing evidence of old lesions. The same process can be seen on the chest. The thighs and arms have only scattered excoriated papules.

Treatment has included administration of sulfonamide drugs and arsenic intravenously, intramuscularly and orally. Many antipruritics have been used, without much help. The patient has no record of preparations or exact dosage used.

The blood count showed a slight leukopenia (4,000 white blood cells per cubic millimeter). There were no eosinophils. There has not been time for a biopsy or other laboratory studies.

DISCUSSION

DR. HARRY L. ARNOLD JR.: I agree that the duration, the general appearance of the eruption and the pruritus are suggestive of dermatitis herpetiformis. The failure to have any remissions (she has never gone even so long as a week without active lesions) is a point against the diagnosis, as is the lack of grouping. Perhaps these inconsistencies should be overlooked, but it could be a factitious condition.

CAPT. IRVING N. HOLTZMAN, M. C., A. U. S. (by invitation): Have you performed a biopsy? Clinically, I do not think that she has dermatitis herpetiformis. She has all the stigmas of a psychoneurotic person. The eruption is generalized, without any grouping, and she has never had any remissions. Unless the diagnosis could be confirmed histologically, I think that the picture is that of neurotic excoriations.

DR. HAROLD M. JOHNSON: I thought of that because of her appearance and manner. However, her entire back is covered with either lesions or scars, even in the inaccessible central portion.

CAPT. IRVING N. HOLTZMAN, M. C., A. U. S. (by invitation): I think that after ten or twelve years a patient may become expert at reaching the entire back.

CAPT. HERBERT LAWRENCE, M. C., A. U. S.: I should object to considering her neurotic manner and appearance in the differential diagnosis, because any severely pruritic dermatosis of this duration is likely to induce neurotic characteristics.

A Case for Diagnosis (Circumscribed Neurodermatitis?). Presented by CAPT. HERBERT LAWRENCE, M. C., A. U. S.

An 8 year old Chinese girl was seen in September 1944, because of a cutaneous lesion on the left cheek, near the nose. This had appeared four years before as a small, scaly, itching macule, which has slowly progressed in size. She has received various types of local treatment and for the last three years has received at sporadic intervals a total of seventeen roentgen ray treatments. At no time has there been any improvement in the appearance of the lesion.

In December 1943 the patient had been seen, complaining of dizzy spells, and after a complete physical examination a diagnosis was made of psychogenic vertigo.

Examination of the skin at this time reveals a sharply circumscribed, lichenified, slightly raised macule about the size and shape of an almond.

DISCUSSION

DR. HARRY L. ARNOLD JR.: I removed a few fragments of scale and found fairly clear evidence of follicular dilatation and plugging. My diagnosis would be discoid lupus erythematosus.

DR. HAROLD M. JOHNSON: That was my diagnosis. The lesion has been aggravated by sunlight.

CAPT. DAVID MUSMAN, M. C., A. U. S.: It does look like lupus erythematosus, but the mother's statement that the lesion occasionally flared up without exposure to sun made me think of a drug eruption or at least of the advisability of excluding that possibility.

CAPT. HERBERT LAWRENCE, M. C., A. U. S.: I almost failed to recognize this lesion today when I saw it. It has changed greatly in the one week that she has been using a tar-containing preparation on it. Originally, it was a simple lichenified macule, which strongly suggested lichen simplex chronicus.

CAPT. L. H. ROSENTHAL, M. C., A. U. S.: Every one has seen many cases of lichen simplex chronicus, but how many have ever seen one of eruption on the face?

DR. HAROLD M. JOHNSON: It is certainly rare there, especially on the cheek. I think that it would be interesting to see whether this child responds to a series of injections of bismuth.

DR. HARRY L. ARNOLD JR.: That would be my recommendation, too.

CAPT. IRVING N. HOLTZMAN, M. C., A. U. S. (by invitation): I see no objection to trying to confirm the clinical diagnosis by biopsy.

PHILADELPHIA DERMATOLOGICAL SOCIETY

Carmen C. Thomas, M.D., *Chairman*

Reuben Friedman, M.D., *Secretary*

Dec. 15, 1944

Bilateral Matured Cataracts Complicating Atopic Dermatitis. Presented by DR. MEYER L. NIEDELMAN.

N. G., a white woman aged 28, presents persistent symmetrically distributed dry, scaly excoriated lesions over the face, neck, chest, back, thorax and cubital and popliteal areas and the thighs. Some of the areas are exudative. The dermatitis first appeared at the age of 5 years. It began in the cubital and popliteal areas and spread to the present sites. The patient states that she had good vision until one month after the birth of her baby, three months ago, when she noticed dimness of vision, cloudiness and inability to distinguish objects. This condition has progressed rapidly until at present she is able to distinguish only light and that faintly. The cataracts in both eyes are fully matured. Her mother had infantile eczema, and a first cousin, 20 years of age, has eczema.

The serologic reaction of the blood for syphilis was negative. A urinalysis gave normal results. The blood sugar was 82 mg. per hundred cubic centimeters. A complete blood count revealed 76 per cent hemoglobin, 4,540,000 erythrocytes and 8,500 leukocytes with 59 per cent neutrophils, 28 per cent lymphocytes, 1 per cent monocytes, 11 per cent eosinophils and 1 per cent basophils. The patient has had extensive treatment by various methods with little benefit.

DISCUSSION

DR. FRANK C. KNOWLES: There ought to be an expression of opinion about how frequently this complication is seen in atopic dermatitis. It is the first one I have seen, and I think that it is rare. Although it is cited as a complication, it is seen so infrequently that to my mind it is a question whether it is a complication or simply a coincidence.

DR. J. M. SCHILDKRAUT, Trenton, N. J.: I encountered a similar case, that of a boy with atopic eczema, who had a cataract in one eye which was thought to be a mere coincidence, but I think that such a situation happens too frequently. One reads of it in the literature continuously. There must be some relation between the eczema and the cataract.

DR. CARROLL S. WRIGHT: I tried to find out whether the patient had had roentgen ray therapy, because ophthalmologists sometimes say that roentgen rays

around the eyes may produce cataracts. She said that she had never had anything but ultraviolet rays, but I should like to ask Dr. Niedelman whether she has ever had roentgen rays.

DR. MEYER L. NIEDELMAN: No, she has had only ultraviolet rays.

DR. CARROLL S. WRIGHT: I have never seen how roentgen rays, in the very small doses used around the eyes, could produce a cataract.

DR. SIGMUND S. GREENBAUM: I do not think that this is atopic dermatitis, although it is often called that. I think that the patient's atopy or allergy disappeared a long time ago and what one sees now is the result of an unstable cutaneous nervous system. She has a central (thalamic) feeling of pruritus, and as a result she has a habit of scratching which eventually follows improperly or injudiciously treated cases of atopic or allergic or true infantile eczema. I feel that her skin if left alone would become perfectly normal. Years ago, when cutaneous tests became popular, I did them in many of these cases and found many positive reactions. Then I deliberately prescribed for the patients the foods to which they were supposedly sensitive, but they did not get worse; and when they discontinued those foods, they did not get better.

DR. HERBERT J. SMITH: I treated this woman about a year ago when she was pregnant, and her dermatitis cleared up. She had no trouble with her sight at that time and certainly no evidence of cataract. I agree with Dr. Knowles that I have never seen atopic eczema in association with cataract, but from the literature I gather that the conditions occur together in about 10 per cent of cases.

DR. SIGMUND S. GREENBAUM: I believe that such cases are few and far between. I agree with Dr. Knowles that the cataract is coincidental, not a complication of the atopic dermatitis.

DR. J. M. SCHILDKRAUT, Trenton, N. J.: Some of the ophthalmologists tell me that there is some relationship between eczema and cataract and that it is more frequent now than in the past.

DR. MEYER L. NIEDELMAN: The ophthalmologist who referred the patient to me was one of the chiefs at the Wills Hospital for Diseases of the Eye, and he stated that he has seen several similar cases. L. A. Brunsting (ARCH. DERMAT. & SYPH. **34**:935 [Dec.] 1936) recorded 101 cases, in 10 of which there were cataracts, which seems to me a little high. In most of the reported cases the cataracts were of the juvenile type. Surprisingly, in this woman the cataracts have matured rapidly indeed, so that at present she can barely see light. She will be operated on next week.

Dermatitis Herpetiformis Followed by Lesions Resembling Lichen Planus. Presented by DR. A. G. PRATT.

B. G., a white woman aged 23, presented grouped vesicular lesions of various sizes on the legs, arms and trunk on admission to the hospital. These rapidly dried and were followed by lesions suggesting lichen planus, especially on the extremities. There was no outbreak on the head. (Since the foregoing statement was written, vesicles have reappeared.) Twenty months ago red macules followed by vesicles appeared on the feet and spread to the arms and trunk. Itching was severe. After treatment by local physicians the patient entered the hospital in February 1944 and in two weeks was discharged free of all traces of any cutaneous disorder. The vesicles had rapidly disappeared and were succeeded by flat purplish shiny lichenoid lesions, which in turn disappeared. A month later there was a relapse. Vesicular and bullous lesions again appeared. Under her upper plate on the soft palate a bulla developed, followed by superficial erosion. The patient is a well nourished woman, the mother of two children, the last of whom was born just before the cutaneous trouble started. Her general health is good. The upper jaw is edentulous. The heart and lungs are normal, as are the temperature, pulse and

respiration. The tonsils are much enlarged and partly covered with a whitish exudate.

Studies of the blood revealed normal conditions, except for a leukocyte count of 16,500 on two occasions. The Wassermann and Kahn reactions of the blood for syphilis, on Feb. 19, 1944, were negative. On November 30, the Wassermann reaction was again negative. A roentgenogram of the chest showed no tuberculosis.

On the patient's first admission to the hospital, in February 1944, she was given only solution of potassium arsenite U. S. P. by mouth. On her admission on November 24, she received sulfadiazine and sodium bicarbonate, 1 Gm. of each every four hours for twelve days. Solution of potassium arsenite in ascending doses to 5 minims (0.31 cc.) three times a day was also administered.

DISCUSSION

DR. BERTRAM SHAFFER: I suggest that this eruption may be a bullous lichen planus.

DR. FRED D. WEIDMAN: I understand that at the hospital, with a galaxy of experienced dermatologists, it was agreed that this was a classic case of dermatitis herpetiformis. It seems to me tonight that this is not lichen planus but only a lichenoid eruption. I think that this case was primarily one of a circinate eruption of dermatitis herpetiformis with clearing in the center and that it is the acuteness of the processes around the vesicles which has led to a larger amount of inflammatory residuum than is usually seen in cases of dermatitis herpetiformis and that the papules that are now seen represent an inflammatory residuum of the dermatitis herpetiformis. The eruption has the distribution of erythema multiforme; I have long thought that dermatitis herpetiformis in the final analysis, (that is, from the standpoint of pathologic processes) is of the order of an erythema multiforme. That would tie in with this case and account for the distribution of the peripheral papular features.

DR. ISADORE ZUGERMAN: I agree with Dr. Weidman that if this eruption were lichen planus one should expect to find lichen planus lesions elsewhere than in areas where the bullous lesions were previously found. It does not seem that this has occurred. Solution of potassium arsenite and sulfonamide compounds may originate bullous eruptions in some cutaneous diseases. Erythema multiforme could have been the original form of this disease, with sulfadiazine and the arsenic originating and continuing the bullous lesions.

DR. FRED D. WEIDMAN: I suggest in cases like this that investigations be made for focal infections. One of my patients for whom Dr. Schamberg and others had made a diagnosis of dermatitis herpetiformis was found at necropsy to have had suppurative bronchiectasis, which had escaped diagnosis. That is, there was a focus of infection which had been operating in the patient for years.

DR. CARMEN C. THOMAS: There is a note that the tonsils are much enlarged and partly covered with a whitish exudate.

Parapsoriasis Varioliformis. Presented by DR. HENRY B. DECKER.

P. R., a white youth aged 18 years, had an eruption in March 1944 which was diagnosed as varicella. He suffered a recurrence in October 1944.

DISCUSSION

DR. HERMAN BEERMAN: I consider this a case of Mucha-Habermann's disease. It is the first to be presented here in several years.

DR. CARMEN C. THOMAS: What have the members found most effective in the treatment? This patient has had no treatment.

DR. SIGMUND S. GREENBAUM: Time.

DR. HERMAN BEERMAN: In 1 case, time and ultraviolet rays helped the patient.

DR. FRANK C. KNOWLES: I think that the term "parapsoriasis" is unfortunate. In the past it was practically a dumping ground for almost every disease of the

skin, whether dry or moist, which one did not know exactly where to place. Such a group disease one puts under the heading of parapsoriasis, without any effort to find an appropriate term to describe the lesions. To my mind to place dry, vesicular and pustular eruptions under the one heading is unfortunate. I think that parapsoriasis should be limited to a special entity.

Fixed Eruption (Arsenic; Bismuth?). Presented by DR. BERNARD L. KAHN.

I. S., a Negro woman aged 22, presents a multiform macular circinate eruption of the face and body. She received antisyphilitic therapy when she had secondary syphilis. The last course of the bismuth compound was completed May 4, 1944, and the last course of oxophenarsine hydrochloride (mapharsen) was completed on November 30. After forty-two doses of bismuth subsalicylate and forty-four of arsenicals, a fixed eruption developed over the face and body. She has not yet received treatment for the eruption.

The serologic reaction of the blood for syphilis was negative on Nov. 30, 1944. The spinal fluid was negative for syphilis on Nov. 22, 1943. A complete blood count was essentially normal.

DISCUSSION

DR. FRANK C. KNOWLES: I think that this is not an eruption due to bismuth. Inasmuch as this woman has been taking an arsenical as well as a bismuth preparation, the eruption should be regarded as of arsenical origin rather than as due to bismuth. I believe that bismuth does not give rise to any fixed types of eruption. This patient presents no involvement of the mucous membranes and no pigmentation such as often is caused by bismuth.

DR. HERMAN BEERMAN: I have yet to see a real fixed eruption which could be proved to be due to bismuth, but I have seen such an eruption in patients who have received bismuth, though whether or not it was due to bismuth, I do not know. According to Dr. Abramowitz and others, almost anything will produce a fixed eruption. They even speak of a drugless fixed drug eruption. They speak of a fixed eruption due to magnesia magma. If that can produce it, I see no reason why bismuth cannot.

DR. FRANK C. KNOWLES: I do not think that one should attribute an eruption on the skin to any one drug if more than one drug is being taken. As long as one knows that fixed eruptions may be present over a period of months, it does not follow that the drug being taken at the present time is the cause; the eruption may be due to a drug that was taken immediately previously.

DR. LOUIS GOLDSTEIN: I think that a simple test would be to give the patient a rest and then give an arsenical and a bismuth compound separately and see which aggravates the eruption.

DR. HERMAN BEERMAN: Recently I saw a man who in 1937 had a bullous eruption which subsequently became pigmented. Not long ago, he took phenolphthalein and reappeared on account of a new eruption. It was definitely shown that he had taken phenolphthalein, and in a short time he died. Fatal results from drug eruptions must be kept in mind when one is considering proof of the cause of the eruption by readministering the suspected preparation.

A Case for Diagnosis (Scleroderma; Atrophoderma; Acrodermatitis Atrophicans Chronica?). Presented by DR. J. M. SCHILDKRAUT, Trenton, N. J.

M. F. R., a white woman aged 40, of good general appearance, presents on the anterior surface of the left thigh a palm-sized area, ivory colored and hard on palpation. A similar patch is present on the dorsum of the left foot. In addition, the skin of the thigh and leg is thin, atrophic, dusky red and scaly, and these conditions extend over the lower portion of the abdomen. There is also pain in the left leg. The hardened areas are softening, but the atrophic condition is spreading. The dermatosis began in July 1943.

DISCUSSION

DR. SIGMUND S. GREENBAUM: One observes sclerodermatous lesions in acrodermatitis atrophicans chronica as well as calcified and fibrous nodules.

DR. FRED D. WEIDMAN: Morphea really fits the case better. One might try bismuth subsalicylate, which Dr. Klauder has been employing after a lead by Dr. Stokes.

DR. J. M. SCHILDKRAUT, Trenton, N. J.: The patient has been treated with a neostigmine salt. I think that the lesions are somewhat softer. Associated with the atrophy there is a quasi-ichthyotic condition, for which I gave her vitamin A. She complains of severe pain in the leg. I have also given her estrone. How is the bismuth compound given?

DR. HERMAN BEERMAN: In the same way as bismuth subsalicylate. Dr. Stokes spoke of a French report which concerned bismuth hydroxide, but Dr. Klauder's case illustrates the fact that one may use other bismuth compounds; apparently it is the bismuth that effects the improvement.

DR. CARMEN C. THOMAS: This patient complains of considerable pain from the cold of the floor, and I wonder whether the pain is not due to vasospasm.

NEW YORK DERMATOLOGICAL SOCIETY

Hans J. Schwartz, M.D., *President*

George C. Andrews, M.D., *Secretary*

Dec. 19, 1944

A Case for Diagnosis (Pigmentation of Lip and Buccal Mucosa). Presented by DR. JOHN C. GRAHAM.

Mrs. I. R., 51 years, is a graduate nurse. About two years ago she first noticed a pigmented spot on the right side of the lower lip, inside the vermilion border. Similar spots have spread gradually to involve other parts of the mucosa of the lower lip and the buccal mucosa of both cheeks to some extent. There have been no subjective symptoms. Neither has there been any history of drugs applied locally or taken internally.

The pigmented areas are not indurated, and they appear normal in every way except for the deposit of pigment, which is increasing in extent. The individual patches are not getting darker. The principal complaint is the disfigurement.

DISCUSSION

DR. A. BENSON CANNON: For many years I have frequently observed patients with such brown pigmented spots on the mucous membranes of the lips and mouth, most of these patients giving a history of having received arsenic. The pigmentation is superficial, and I have successfully removed the areas by lightly desiccating them with the electric needle. Several years ago Dr. Pusey reported similar cases (ARCH. DERMAT. & SYPH. **36**:613 [Sept.] 1937) in his article on pigmented spots of the mucous surface of the lips. I think that the blood and the urine should be examined for arsenic. If the patient objects to the appearance of the pigmented spots, they can always be removed with the electric needle.

DR. MAURICE J. COSTELLO: I have seen this type of pigmentation on several occasions following bismuth therapy.

DR. GEORGE M. MACKEE: I have been interested in this pigmentation as occurring in the mouth, the vagina and the anal mucosa. While some might be due to heavy metal or arsenic retention, I am more inclined to think of a nevoid defect or a rudimentary pigmentation. In this connection, the skin and the mucous membranes of many mammals are heavily pigmented.

DR. JOHN C. GRAHAM: To the best of my knowledge, this patient has had no heavy metals. She is intelligent, and close questioning has not brought out any history of any heavy metals. She may have received arsenic from some extraneous source. She lives on the eastern end of Long Island, where large quantities of potatoes are raised. In potato culture large quantities of arsenic are used, and it may be possible that over the years the patient has absorbed arsenic from the dust in the air. Other than that, I cannot possibly account for it.

A Case for Diagnosis (Tuberculoderma?). Presented by DR. FRED WISE.

P. I., a girl aged 14 years, was referred by Dr. T. W. Baer, of Pittsburgh. At the age of 5 years she had scarlet fever, and shortly after this subsided what appeared to be a papular rash developed. As this eruption subsided, it left bluish, atrophic discolorations on her arms and legs. During the fall of 1940 she had chorea. In March 1942 she had rheumatic fever. This was followed by severe pains in the calves of both legs and the shortening of the achilles tendon of each leg. In September 1942, during her hospitalization, the Kahn reaction of the blood was negative. Spinal fluid examination gave the following findings: the cell count was 1; the globulin reaction was negative; the Wassermann reaction was negative, and the colloidal gold curve was 000000000. The basal metabolic rate was —2 per cent. A roentgenogram of the bones revealed the sella turcica as normal, as were the bones of the legs. A roentgenogram of the chest showed no abnormality.

On Sept. 15, 1942, a biopsy of the skin from the left calf was taken, with the patient under anesthesia with procaine hydrochloride; the section did not reveal any definite findings. On September 22, tenotomy of the achilles tendons was performed. Subsequently, with the finding of an endocarditis, a tonsillectomy was performed and it resulted in apparent clearing of the clinical cardiac findings.

The patient was under the observation of Dr. Baer since Oct. 7, 1944, at which time she presented large ulcerations on the extensor surfaces of both legs. These ulcerations would increase in size, heal in one area and break down in another, until final healing of the involved sites occurred after five weeks.

On Nov. 24, 1944, the patient reported that while sitting in school on November 22 she felt a burning sensation over the extensor surfaces of both arms and legs, and, on examination, fresh lesions were found on these areas. The lesions appeared as erythematous patches on the extensor surfaces of her arms and legs. The areas quickly formed what seemed to be iris type lesions. The central portions became bullas, which were filled with viscous, hemorrhagic material. After the overlying skin was drained, the resulting lesion was a moderately deep ulcer.

The patient received ¼ unit of unfiltered roentgen rays to all the involved sites at each office visit. She has been given weekly injections of crude liver extract. Oral medication consisted of the following: mixed vitamins and, from November 24 to December 9, sulfadiazine tablets, 7.7 grains (49 Gm.), taken four times a day. From December 9 to the time of this presentation she has taken the sulfadiazine twice daily.

DISCUSSION

DR. GEORGE M. MACKEE: I cannot make a diagnosis but lean definitely to some type of tuberculosis or tuberculid. I saw one elementary lesion which was a small, deep-seated nodule.

DR. GEORGE C. ANDREWS: I agree with Dr. MacKee. I feel that the lesions on both the legs and the arms look like tuberculids.

DR. MAURICE J. COSTELLO: I agree with the previous speakers. More specifically, I believe that she has tuberculous gummas independent of underlying tuberculous foci. I also noticed a peculiar atrophy of the cheeks, which I believe is associated with the other lesions.

DR. A. BENSON CANNON: I suspect that the lesions are self induced. I have never seen a dermatologic disease similar to the lesions present in this case, nor

have any of the former investigators been able to make a diagnosis clinically or from their laboratory investigations. The child has spent most of her life in various hospitals and has the background (psychologically) for self induced lesions. The ulcers are certainly traumatic in type. Her actions and facial expression as she entered the room caused me to suspect that she might be a malingerer. I believe that if a plaster cast were put on the extremity all the lesions would heal.

DR. FRED WISE: The patient had been previously presented before several dermatologic groups in Pittsburgh, but no definite diagnosis had been established. I am in agreement with the opinions expressed by other members that the eruption is in all probability a form of tuberculosis or tuberculid, but I am unable to reconcile such a diagnosis with the extensive scarring on the skin of the knees. I regret that Dr. Cannon's suggestion as to diagnosis does not appeal to me in this instance.

DR. GEORGE M. MACKEE: I agree with Dr. Wise that this is not a self induced eruption. There are innumerable papules on each cheek and atrophy. Another interesting feature is the eruption around the elbows and knees.

Xanthoma Tuberosum; Keloid; Jacquet Posterosive Syphiloid. Presented by DR. GEORGE M. LEWIS.

J. H., a 4 month old infant, was first seen on Dec. 1, 1944 at the skin clinic of the New York Hospital. According to the mother, three weeks after birth several reddish yellow lesions appeared in the inguinocrural region. This was followed by the appearance of similar elevations on the scalp and trunk about two weeks later. Since that time, no new lesions have appeared and the old ones have remained stationary. In both inguinocrural folds there was diffuse erythema. On the right side of the vulva and on the right buttock are round, reddish yellow, slightly eroded nodules, about 3 by 2 cm., under the left costal margin, and in the right parietal region are firm, yellowish red papules about 1 by 2 cm. The blood from the cord gave a negative serologic reaction. A dark field examination from an eroded lesion was negative. The mother's blood gave a negative reaction to the Wassermann test.

DISCUSSION

DR. MAURICE J. COSTELLO: Lesions occurring in the diaper region have been described as similar to condylomas, and I believe that these are pyogenic lesions simulating condylomas.

DR. GEORGE C. ANDREWS: I was impressed by the yellow, lemon color of the lesions of the scalp and believe that they are juvenile xanthomas and that the other lesions will become yellowish. If this is true, it is better not to treat them. I have had 2 cases in which juvenile xanthoma disappeared when the children reached 4 or 5 years of age. Some patients have been helped by thyroid extract.

DR. GEORGE M. MACKEE: I agree with Dr. Andrews.

DR. FRED WISE: I agree with Dr. Andrews also. I have an idea that fibroxanthoma is being dealt with. McDonagh described similar cases, and I think that it is possible that these lesions might turn out to be xanthoendothelioma. I suggest that a biopsy may offer additional evidence.

DR. A. BENSON CANNON: I should first attempt to rule out bromides as the cause. I have seen several cases of infants born with bromide tumors that were identical to this, and I should think that an estimation of bromide in the blood and the urine should be made.

DR. FRANK C. COMBES: I agree with Dr. Wise. McDonagh called these nevoxanthoendothelioma. They are probably neither nevi nor endotheliomas although they are xanthomatous.

DR. FREDERICK REISS (by invitation): At the time the child was presented, the lesion in the inguinal region looked suggestive of posterosive syphiloid, but in the past few weeks the condition has definitely changed and the lesions in the inguinal

region are similar to those in the occipital and parietal region. I think that this is possibly a case of xanthoma or nevoxanthoendothelioma.

A Case for Diagnosis (Sarcoid; Leprosy?). Presented by DR. FRED WISE.

Mrs. P. L., a married woman aged 49 years and a native of Nassau, West Indies, was under the care of Dr. Frances Pascher, of Brooklyn. The patient had a generalized macular, nodular and tuberous eruption, which first appeared about ten years previously. She had lived in this country since childhood.

Her history indicated that she had been hospitalized for a period of seven weeks and that a diagnosis of Hodgkin's disease (lymphogranulomatosis) was made in 1935, based on two biopsy examinations. She received daily roentgen ray treatments for ten days while in the hospital.

In the past two years, Dr. Pascher's investigations revealed the following findings: a biopsy of a nodular lesion on the abdomen showed the characteristic changes of Boeck's sarcoid; a roentgenogram of the lungs was normal; examination of the hands on Jan. 4, 1943, showed changes suggestive of rarefication of the head of the proximal phalanx of the first finger of the right hand and the head of the second metacarpal bone; the Wassermann reaction of the blood was negative, and quantitative tests with tuberculin showed an anergic response.

On presentation, examination showed a widespread eruption involving the head, face, trunk and extremities. The lesions were most abundant on the back and extremities; they consisted of flat plaques, nodules and tumefactions of reddish brown and coffee color; on the wrists, the individual lesions were tuberous and most prominent. The outer aspects of the eyebrows were devoid of hair; the cervical lymph nodes on the right side of the neck were enlarged; there was a moderate grade of interosseous atrophy of the knuckles of the hands but no evidence of thickening of the palpable nerve strands. Tests for presence of anesthesia of the skin were negative. (Tests for heat and cold sensation were not reported at the time of presentation.) Search for the microbacillus of leprosy was fruitless. The patient had lost about 20 pounds (9.1 Kg.) in the past two years.

Unfiltered roentgen ray therapy combined with subcutaneous administration of arsenic, given two years previously, had resulted in complete resolution of the cutaneous lesions, with the exception of the tuberous lesions on the wrists. The present attack, however, has failed to respond to roentgen therapy.

DISCUSSION

DR. GEORGE M. MACKEE: This may be a case of leprosy, but this is such a serious diagnosis that it is necessary to prove it by finding the bacillus of Hansen and also by ruling out sarcoidosis. The eruption shows hyperesthesia instead of hypoesthesia. The persistent pruritus may be merely an essential pruritus.

DR. GEORGE C. ANDREWS: Every once in a while a disease is seen which is extremely difficult to diagnose. This looks like leprosy; yet it may turn out to be sarcoid. A diagnosis should not be made until the histologic report is received.

DR. GERALD F. MACHACEK: I saw this woman about eight years ago at the Roosevelt Hospital. Although I suspected leprosy at the time, I assumed that she had not been to the West Indies. The outstanding symptoms were intense pruritus and glandular swelling. She presented only an occasional lesion on the abdomen and thighs. A lymph node was removed, from the sections of which a diagnosis of Hodgkin's disease was made. I saw sections from the abdominal cutaneous lesions and, suspecting leprosy, stained some by Ziehl-Neelsen's technic but discovered no bacilli and finally concluded that the lesion was a lymphoblastic infiltration with tuberculoid structure, particularly as there were not many epithelioid cells present. Although pruritus continued to be the outstanding complaint, the signs of nerve involvement have since developed. Last month the patient noticed a foot drop of the right extremity. She has had ulcerations but no nerve symptoms except hyperesthesia or pruritus. Her case must be reevaluated. It is probably

leprosy, but there is a remote possibility of a tuberculoid lymphoblastoma involving the nerves.

DR. MAURICE J. COSTELLO: The features presented in this case favor both leprosy and sarcoid. I should favor the latter diagnosis because of the patient's failure to react to the intradermal injections of tuberculin. The foot drop may be due to some bony changes in the sacrum, with indirect pressure on the lumbosacral region.

DR. FREDERICK REISS (by invitation): There are certain features of leprosy which I should want to correlate with this eruption. The clinical features, especially the nodules, are suggestive of leprosy, but the histologic changes, as interpreted by Dr. Sims, would be a contraindication in such extensive formation of nodules. In tuberculoid leprosy, the sensory changes would be more prevalent than they are in this case. As Dr. MacKee pointed out, there is more or less hyperalgesia. That would not be in accordance with what is known of tuberculoid leprosy. Changes in the bone could, of course, occur in tuberculoid leprosy, but without corresponding clinical findings I think that it would be rather difficult to entertain this diagnosis. Moreover, if this is the nodular type of leprosy, sensory changes could be absent, and in that case an entirely different picture would be expected; in addition, leprosy bacilli would be easy to find.

DR. FRANK C. COMBES: I agree with everything Dr. Reiss has said. There is not a tremendous difference in the biologic actions associated with sarcoid and the tubercular type of leprosy; blood changes and bony changes are similar, although there are certain distinguishing features. I should spend all my time in this case looking for Hansen's bacillus.

DR. A. BENSON CANNON: I am convinced that the patient has leprosy. I have seen patients with leprosy with just as many lesions as this patient has, and the enlargement of the lips, lobes of the ears, eyebrows, wrinkling of the forehead, the brownish red, soft tumors, the large ulnar nerves and the foot drop are all characteristic symptoms of leprosy. Itching and hyperesthesia are common symptoms in nodular leprosy. Dr. Kellersberger, of the American Mission to Leprosy, in a personal communication, stated that Pron, a new sulfur derivative, has given the greatest hope of success in the treatment of leprosy of any remedy yet used. He stated that Pron has been in use at the leprosy colony in Carville, La., for the past few years and has proved to be beneficial in the treatment of certain types of the disease. Pron should be of benefit in this type of leprosy. I feel reasonably certain that if careful search is made for Hansen's bacilli they will be found.

DR. GEORGE C. ANDREWS: I have corresponded recently with Dr. Guy H. Faget, in charge of the United States Marine Hospital (National Leprosarium) in Carville, La., concerning the use of Diasone (disodium formaldehyde sulfoxylate diaminodiphenylsulfone) and Promin. He stated that the results of treatment with Diasone thus far are similar to those obtained with Promin, which has an inhibitory action on the progress of the disease. Although he has been using these drugs for about five years, it is still too early to form any definite opinion as to their mode of action and their limitations in such a chronic disease as leprosy. The action is slow, and benefits do not become manifest until after six months of therapy. Benefits are shown more rapidly with Diasone than with Promin, but, on the other hand, the ulcerative complications, keratitis and laryngitis, do not respond so readily.

DR. MAURICE J. COSTELLO: The patient has lesions on the scalp, which is extremely unusual in leprosy. Have roentgenograms of the lungs been taken?

Sycosis Vulgaris (of Ten Years' Duration). Presented by DR. HOWARD FOX.

P. J. G., aged 33, a truck driver of Italian extraction, has suffered from an eruption of the bearded region for the past ten years. At the onset, the patient said, there were individual pustules, which eventually changed to the present type of eruption.

He now presents a dry, scaly eruption involving the entire surface of the bearded area and that of the upper lip. He is an intelligent man and is apparently a cooperative patient.

He has been treated by other physicians, with many remedies, but without permanent effect. He said that the best results were obtained from a dozen weekly treatments with roentgen rays. At no time were roentgen rays used to cause epilation. Other methods of treatment included ultraviolet irradiation, mechanical epilation by "Zip"-methods, staphylococcic vaccines, ammoniated mercury ointment, boric acid ointment, gentian violet medicinal, penicillin given intramuscularly (total of 1,000,000 units) and compound chlorohydroxyquinoline ointment, which he has used daily for a year. He has had no sulfonamide drugs. The eruption is only partially improved by chlorohydroxyquinoline ointment.

The patient is presented for therapeutic suggestions.

DISCUSSION

DR. GEORGE C. ANDREWS: I should suggest the use of sulfadiazine internally.

DR. GEORGE M. MACKEE: Recently I have had several patients with sycosis vulgaris of twenty years' duration. The lesions had resisted all conventional therapy, including sulfanilamide drugs, roentgen rays and penicillin by injection but cleared up in a few weeks with penicillin ointment, 500 Harvard units to the gram. The vehicle seems to make little difference. I have used Aquaphor, hydrous wool fat and modern greaseless creams as vehicles, with equally good results.

DR. GEORGE C. ANDREWS: I have had similar results with penicillin ointment, using different bases, in a strength of 500 units. It certainly gives remarkable results in sycosis vulgaris.

DR. GEORGE M. LEWIS: A patient has been hospitalized at the New York Hospital who had sycosis incidentally, and when penicillin was administered for another disease the sycosis promptly responded. I am still waiting for the eruption to return. It is now well over a month, and the condition has not yet relapsed.

Hemangiopericytoma. Presented by DR. FRED WISE.

P. C., a boy aged 4, registered at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on July 18, 1944, presenting a growth on the nose, of one year's duration. It began as a pinhead-sized node, which gradually enlarged to its present size.

On the base of the columella of the nose is a pea-sized, smooth, firm growth, red and well defined, resembling an angioma.

Histologic section examined by Dr. Charles F. Sims was diagnosed as hemangiopericytoma. The description is as follows: "Throughout the upper, middle and deep corium is a diffuse and ill defined cellular mass. Throughout this mass one may note many dilated vessels, with lumens of varying size. Surrounding these vessels and fusing with those of neighboring vessels are many spindle-shaped cells with rather large round or oval hyperchromatic nuclei and poorly defined cytoplasm."

DISCUSSION

DR. GERALD J. MACHACEK: By pericytoma the pathologist means a tumor composed of cells found in the walls of blood vessels. Morphologically, this tumor is composed of spindle cells and is probably benign.

DR. GEORGE C. ANDREWS: There was a tumor precisely like this on the chin, described by Stout, under the title of "angiopericytoma" with microscopic features which, of course, are just the opposite of those of hemangioendothelioma. Whereas the latter arises from the endothelium, this tumor arises from the adventitia of the blood vessel. Like the hemangioendotheliomas in children, they are benign.

DR. GEORGE M. MACKEE: I saw this section only under low power, and it is my impression that the infiltrating cells are fibroblasts. I wonder whether it might

not be an angiofibroma. I recommend excision or leaving it alone. There is too much fibrous tissue formation for the use of radium.

A Case for Diagnosis (Lichen Chronicus Simplex with Nodular Growths).
Presented by DR. FRED WISE.

J. B., a white woman aged 29, registered at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Sept. 12, 1944, presenting lesions on the hands since 7 years of age. Her twin sister is not so affected. The patient had infantile eczema of the scalp and face at 8 months. At 7 years she had dry, scaly patches in the cubital areas. She complains of some itching, worse when oozing. Her state of health has been good.

The eruption began as a rough, itchy and scaly patch on the dorsal surface of the right little finger. At 12 years the middle finger of the right hand, at 13 the rest of that hand and at 14 the left hand became similarly affected. This eruption sometimes partially regressed, but it recurred. She received roentgen ray treatments since 1930 to the dorsal and palmar surfaces of the hands and the cubital and popliteal regions, but more to the hands, every two weeks at irregular intervals for a period of two years. In 1932 she was treated with ultraviolet and carbon arc exposures and, later, with injections in the scapular region. In 1937 a matchhead-sized growth first appeared on the dorsal surface of the right middle finger. Within a few months others developed on the same finger. They gradually appeared on the dorsal surface of the right hand during the succeeding seven years. Some months later similar lesions appeared on the left hand. For the past two years the patient has been having "heart burn and gas." Gastric analysis and a hemogram in January 1945 were said to be normal. The eruptions on her hands became aggravated after she ate chocolate and too much meat, fish and cheese. The patient stated that for the past two months she has noticed that if she stays on a diet with a low phosphorus content and takes calcium phosphate, calcium gluconate and vitamin D wafers three times daily the oozing stops and her hands "would be better."

On the dorsal surfaces of the hands, fingers and wrists are fairly well defined, hard, hemispherical white nodules, isolated and closely grouped, varying from the size of pinheads to that of matchheads and split peas. They are painless, raised, smooth and symmetrically distributed, mostly on the dorsal surfaces of the hands and wrists. The skin of the entire dorsal surfaces of the hands, fingers and wrists is thickened, less elastic, moderately infiltrated and covered with ill defined scaly patches. There are numerous fissures, most pronounced on the knuckles. The palmar surfaces are comparatively free except for some fissuring and crusting in the creases. There are lichenified patches and eczematized, fairly well marginated patches in the cubital and popliteal areas, with exaggerated markings on the skin, fissuring and crusting on erythematous bases and mild lichenified patches on the neck. On diascopic pressure the nodular growths are partially compressed, revealing uniform white spots. Atrophy and telangiectasia were not present.

The urine was normal. The hemogram was normal except for 4 monocytes and 8 polymorphonuclear eosinophils.

Two nodules were excised and examined histologically by Dr. Charles F. Sims. The interpretation is as follows: "The epidermis is moderately and fairly regularly acanthotic. Throughout the upper corium and midcorium is a diffuse cellular reaction, composed of rather large cells with poorly defined cytoplasm. Between these cells the collagen has undergone a degeneration which suggests the edematous and granular type. Many fibroblasts are scattered throughout the zone. The findings suggest a degenerative process which cannot be placed in a definite category. While some of the features are in part suggestive of granuloma annulare, they are by no means definite."

DISCUSSION

DR. JOHN C. GRAHAM: I never heard of such lesions ascribed to roentgen rays. I have no idea what they are.

DR. FRANK C. COMBES: I do not think that these lesions are related to the roentgen therapy that this patient has had. They struck me as being part of the lichenification. She has a great many along the arm, and these impressed me as being lichenized lymphedema.

DR. GEORGE M. MACKEE: The patient apparently has neurodermatitis. The interesting feature is the large papules or nodules. It is possible that these lesions are the result of years of rubbing and scratching and may be nothing but exaggerated lichenification or hypertrophic papules. However, this is not borne out by the histology. I have not seen lesions of this sort before in neurodermatitis. It may be that she might have these lesions even if she did not have neurodermatitis. They resemble the lesions seen in elderly or old people, especially those who have had long, continued exposure to solar rays, in other words, keratosis. This is suggested also by the histology. It is a degenerative process.

DR. PAUL E. BECHET: I have not infrequently observed papules aggregated in patches, with scaling and much thickening of the skin, apparently entirely caused by friction. In one particular instance, in a woman patient, a similar clinical picture was produced by daily friction with a pumice stone for several consecutive years in attempts at removing superfluous hair.

DR. FRED WISE: I am glad to learn that none of the members regard this eruption on the hands as a roentgen ray effect just because there is a history of exposures to roentgen rays for the associated atopic dermatitis. The nodular lesions closely resemble the nodular neurodermatitis described by Kreibich.

A Case for Diagnosis (Bowen's Disease?). Presented by DR. ANTHONY C. CIPOLLARO.

L. P., a Puerto Rican woman aged 64, first attended the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital in the service of Dr. Williams in 1935. About twenty years ago she had a lesion in the perianal area, which was treated with roentgen rays in Puerto Rico. The disease improved but later recurred. When the patient attended the Skin and Cancer Unit, several biopsies were made. One of them showed the lesion to be that of Bowen's disease, and another showed it to be a possible prickle cell epithelioma. The patient was referred to the surgical department, where most of the involved tissue was removed and skin grafts were performed. A proctoscopic examination showed no involvement of the rectum.

This patient was previously presented at the New York Academy of Medicine, Section of Dermatology and Syphilis, on Nov. 6, 1944 by Dr. Eugene Traub.

The patient now presents a lesion affecting the perianal area, which is oval in shape and measures in its greatest diameter about 10 cm. It is elevated, and the surface is cauliflower shaped and granulomatous. Along the edges of the lesion there is some hyperkeratosis. There is no definite pearly border and no definite ulcer formation. The clinical appearance of the lesion is that of a granuloma.

DISCUSSION

DR. GERALD J. MACHACEK: The two slides which Dr. Cipollaro presented differed. One was definitely that of Bowen's disease, and the other was that of an epithelioma forming what appeared to be incomplete epidermal appendages invading the corium. The lesion was evidently Bowen's disease which had become transformed into a classic epithelioma.

DR. GEORGE C. ANDREWS: This is an interesting and unusual case. Bowen's disease does sometimes metastasize, and this lesion may be such.

DR. RAY H. RULISON: This is an interesting case. The disease process is much more advanced than I have ever seen in the past in similar cases.

DR. FRANK C. COMBES: I agree with the diagnosis as presented. One purpose of this presentation was suggestions as to therapy. The only therapy I can conceive

of is excision and further plastic operation. I should like to ask whether the invasiveness of the lesion increases its radiosensitivity?

DR. ANTHONY C. CIPOLLARO: I am glad that Dr. Machacek confirmed the histologic opinions previously given. This patient looked like this prior to her operation in 1935. During the past nine years the disease has been slowly progressive, and there is no evidence of metastasis. I wonder whether irradiation might not be the proper approach at the present time? I am aware of the fact that Bowen's disease is not particularly radiosensitive.

Extensive Lupus Vulgaris. Presented by DR. FRED WISE.

K. K., a Polish working woman aged 54, registered at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Dec. 5, 1944, presenting lesions of fourteen years' duration. She has been in good general health continuously. She has three sons, the oldest 25, living and healthy. One child died of pneumonia at 4 years.

The patient presents an extensive eruption on the face, neck, trunk and extremities. The lesions are dull, yellow-red, rough, painless, nontender and covered with adherent sparse scaling and some crusting. The eruption involves two thirds of the right side of the forehead, both cheeks, the right ear and the retroauricular region and the entire midface, including the nasal mucosa, except for the left ala nasi and the central two thirds of the chin. This eruption is continued uninterruptedly downward, to envelop, except for a 5 cm. area on the left side, the entire neck, ending in a well marginated border curving upward from the manubrium along the infraclavicular lines. There is a total of eight oval and round isolated lesions on the back, varying from 1 to 3 cm. in diameter, and six lesions on the extensor surfaces of the elbows and arms. There is a 7 by 10 cm. growth located on the left cubital region. On the vertex of the scalp is a fairly superficial half-dollar-sized scaly patch.

The lesions on the forehead and right cheek are irregular, because of ill defined nodular growths, most prominent at the borders. They are superficial and evenly distributed along the neck and V area of the chest. The lesions on the trunk and extremities are round and oval, with well delimited borders rising straight above the skin, 2 to 4 mm. in height. The exaggerated ridges and furrows run upward from the raised edges and converge in the center of the shallowed surfaces. They thus resemble closely, except for the color, the appearance of evenly flattened and hollowed dried figs.

A section was examined histologically by Dr. Charles F. Sims. It was diagnosed as lupus vulgaris. The description follows: "The epidermis is somewhat thinned, with flattened rete pegs and corresponding papillary bodies. Throughout the upper corium and midcorium are scattered groups of epithelioid and giant cells surrounded by a moderate cellular infiltration composed of small, round and wandering connective tissue cells."

DISCUSSION

DR. GERALD F. MACHACEK: Isolated cases of lupus vulgaris respond to various types of therapy. I have seen a patient with lupus vulgaris benefited by local injection of chaulmoogra oil. A good many years ago, in spite of Finsen therapy, I saw the best results obtained at the Vienna *Lupus Heilstätte*, resulting from local excision of small lesions. Repeated focal electrodesiccation has also yielded results. In other words, methods which set up local inflammations or result in complete destruction may be successful. In the English literature there are reports of the successful use of injections of starch locally.

DR. MAURICE J. COSTELLO: I tried the method of injections of starch solutions on several patients with lupus vulgaris, with poor results. My suggestion would be to have the patient try to follow a salt-free diet. Otherwise the patient should be left alone. Occasionally, generalized ultraviolet irradiation might be of some help in conjunction with local therapy.

DR. PAUL E. BECHET: I also believe that local destruction in such an extensive eruption is contraindicated. Perhaps a salt-free diet rigidly carried out might prove of some benefit, though my personal experience with it has not been encouraging.

DR. ANTHONY C. CIPOLLARO: The methods of treating lupus vulgaris are not satisfactory. In an extensive eruption such as this, hospitalization and rest in bed, an adequate high vitamin diet, generalized and localized ultraviolet irradiation, tuberculin injections and all other methods which would improve the general health should have favorable results.

DR. FRANK C. COMBES: I agree with Dr. Cipollaro in regard to local treatment. I do not think that it is of any value in patients with lupus vulgaris if they are not amenable to plastic surgery. I should like to see a patient treated with either Promin or Diasone, treatment such as was suggested today in the case of leprosy. I am anxious to see what the results would be.

DR. FRED WISE: While one might argue that in view of the age and apparent good health of the patient it might be best to refrain from treating these extensive lesions, I fear that the patient would merely become a "shopper" from one clinic to another. I believe that attempts at improving the eruption with skin grafts, plastic operation and graded injections of old tuberculin should be made.

Erythema Multiforme. Presented by DR. FRED WISE.

N. P., a barber aged 47, registered at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Sept. 5, 1944, presenting generalized lesions of four months' duration. He gives a history of sunburn. The day after the sunburn he had chills which lasted for a few hours. Three or four days later a rash with "blisters but no fluid in them" appeared. It itched severely the first two weeks of the eruption. Since then the itching has been slight and only in the lower limbs. He stated that he has been a heavy drinker. He gave no history of ingesting any drugs except acetylsalicylic acid for headaches. He did not remember ever having been sick.

The eruption begins as pea-sized patches, and within a few weeks the diameters of some vary in size from that of a cherry to that of a quarter. They then dry and clear in the center, forming a ring. Some remain as such, while others form larger rings. Some lesions last a month, breaking up and leaving irregular spots, while others have persisted since inception. There were lesions in the mouth about two months ago. The patches that have regressed have been mostly on the back, only a few being on the extremities.

The lesions are generalized, symmetric and profuse and are located mostly on the extremities, including the dorsal surfaces of the hands and wrists, the mid-abdomen, the buttocks, the knees and the genitalia. The back, except for the scapular regions, is free, the brownish residual spots still being fairly clearly discernible as the site of the former patches. There are patches on the lower eyelids. The diameter of the lesions ranges from that of a pea to that of a silver dollar and larger. Some, the smaller patches, are round; others are ring shaped or oval shaped, with broad borders. There are larger serpiginous and bizarre-shaped patches due to coalescence of the broken-up ringed lesions. The borders are slightly raised, several millimeters in width and purplish red. The inner halves of the borders of many lesions are covered with whitish fine adherent scaling and crusting. On diascopic pressure some patches do not reveal any change while others show only partial fading.

Routine laboratory tests are normal except for a relative lymphocytosis, the hemogram showing 23 polymorphonuclear eosinophils.

Patch tests gave only a 1 plus reaction to a recently prepared ointment of 30 per cent potassium iodide in petrolatum. Ingestion of 1.0 Gm. of potassium iodide in two doses produced a new crop of lesions, particularly in the nares, the following day.

The histologic section, examined by Dr. Charles F. Sims, was interpreted as "consistent with a possible dermatitis herpetiformis." The description follows: "The epidermis is somewhat irregular, and at several points of the dermalepidermal junctions one may note subepidermic vesiculation. Basal cell liquefaction as well as exocytosis and exoserosis is present. The cells consist of small round polymorphonuclear neutrophils and an occasional eosinophil. Interstitial and parenchymatous edema of the upper collagen may be noted."

DISCUSSION

DR. GEORGE C. ANDREWS: This case fits into the group both histologically and clinically. It is hard to say whether to call it that or erythema annulare centrifugum, which it resembles a little more closely clinically, or whether to call it dermatitis herpetiformis. I do not see at this time any evidence of mycosis fungoides, but it is possible that something like that may develop in the future.

DR. MAURICE J. COSTELLO: I agree with the diagnosis as presented. The late Henry Niles often spoke of a patient with an eruption similar to this which cleared under intramuscular injections of bismuth subsalicylate.

DR. GEORGE M. LEWIS: I do not think that drugs can be entirely ruled out, even with a noncontributory history. Since the lesions are atypical for erythema multiforme, I am in favor of an attempt to get more history in regard to drugs. The presenting diagnosis is the most workable for the time being, but the cause should be looked for in drugs, bacteria or some unknown cause.

DR. PAUL E. BECHET: The annular formation is certainly suggestive of erythema multiforme. However, the annular lesions, particularly about the buttocks, are distinctly grouped, their borders seem raised and there is a suspicious moisture on a few of them, some of which appear vesicular. It struck me that the possibility of a dermatitis herpetiformis should also be considered.

DR. FRANK C. COMBES: I agree with the diagnosis as presented. I do not think that this is either erythema perstans of Darier or dermatitis herpetiformis.

DR. FRED WISE: The tests with 30 per cent of potassium bromide and iodide ointments were only faintly positive, but the eruption flared up after ingestion of potassium iodide. Many vesicular and bullous diseases are prone to become intensified from ingestion of iodides and bromides. In dermatitis herpetiformis the cutaneous test with ointment is of some significance, but it should not be overvalued.

Book Reviews

Electrotherapy and Light Therapy with the Essentials of Hydrotherapy and Mechanotherapy. By Richard Kovács, M.D., Professor of Physical Therapy, New York Polyclinic Medical School and Hospital, New York. Fifth edition. Cloth. Price, $8.50. Pp. 694, with 353 illustrations. Philadelphia: Lea & Febiger, 1945.

The fifth volume of Kovác's excellent book dealing with many aspects of physical medicine is most welcome. As the title implies, special emphasis is placed on electrotherapy and light therapy, though consideration is also given to hydrotherapy and mechanotherapy. In this edition, a new chapter on hypothermy has been added. The important subjects of roentgen and radium therapy have not been included. All chapters have been revised and brought up-to-date and 87 new illustrations have been added and 49 obsolete ones deleted.

The book is divided into five parts, with thirty-seven chapters. Part I discusses fundamental electrophysics and the general conversion and distribution of electricity. Any physicians interested in physical medicine, including the dermatologist, should read this part of the book with great care. The subject is explained in an understandable manner and is well illustrated with diagrams and drawings. Indeed, the entire volume has a wealth of illustrations, including photographs of apparatus. The author has frequently clarified the subject of electricity by comparing it with the flow of water through pipes. One subject about which the average dermatologist knows little, namely the effect of cold in producing frost bite and chilblains, is well discussed under the subject of hypothermy.

Part V, dealing with applied physical therapy, has chapters relating to the use of physical mediums in various specialties. The chapter on dermatologic conditions has brief descriptions of twenty-five diseases and an extended discussion of the treatment of hypertrichosis, both by electrolysis and by the high frequency current. Most of the statements in this chapter are well known to the average dermatologist, and few criticisms can be made of the conservative statements of the author. This reviewer, however, doubts the efficacy of radiation from a cold quartz mercury vapor lamp in improving the appearance of postacne scarring. In the average case of seborrheic keratosis there is rarely need of "thorough desiccation," as in most cases a cure without scarring can be achieved by simply using a sharp curet. The author's statement that "all forms of generalized dermatitis as a rule serve as a contraindication to ultraviolet irradiation" is certainly not true in the reviewer's opinion. Excellent results may be obtained by this method in many cases of generalized eczema and psoriasis.

The great amount of information in the text, in addition to a wealth of excellent illustrations, bibliographies and glossary, makes this a most valuable book for students and practitioners of physical medicine.

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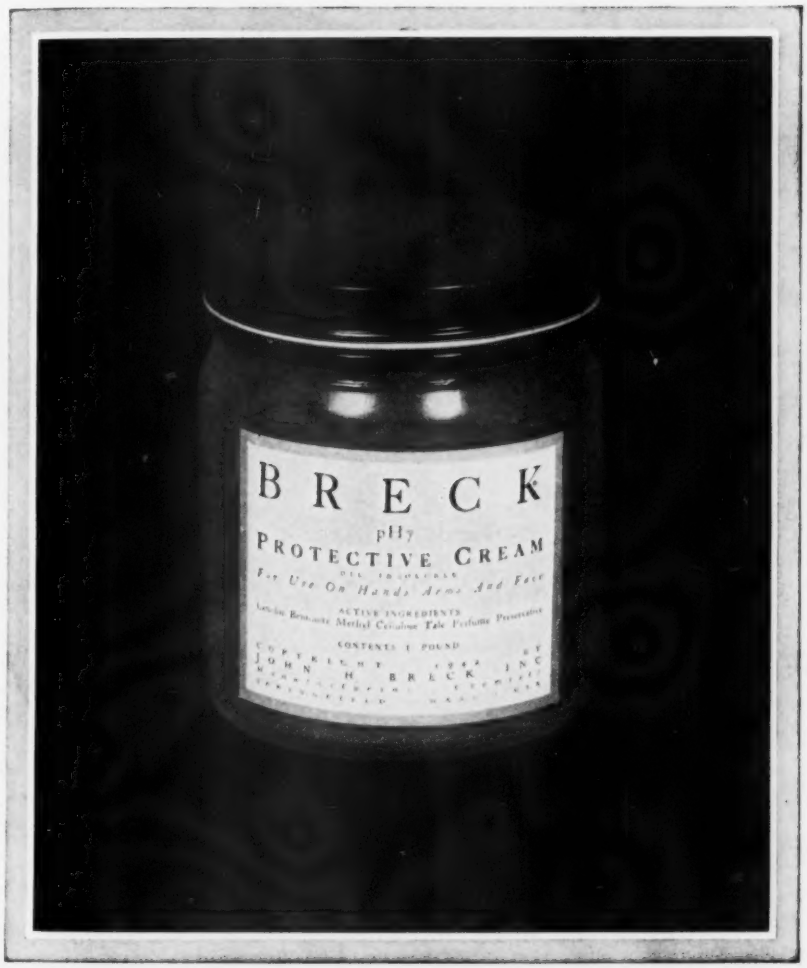

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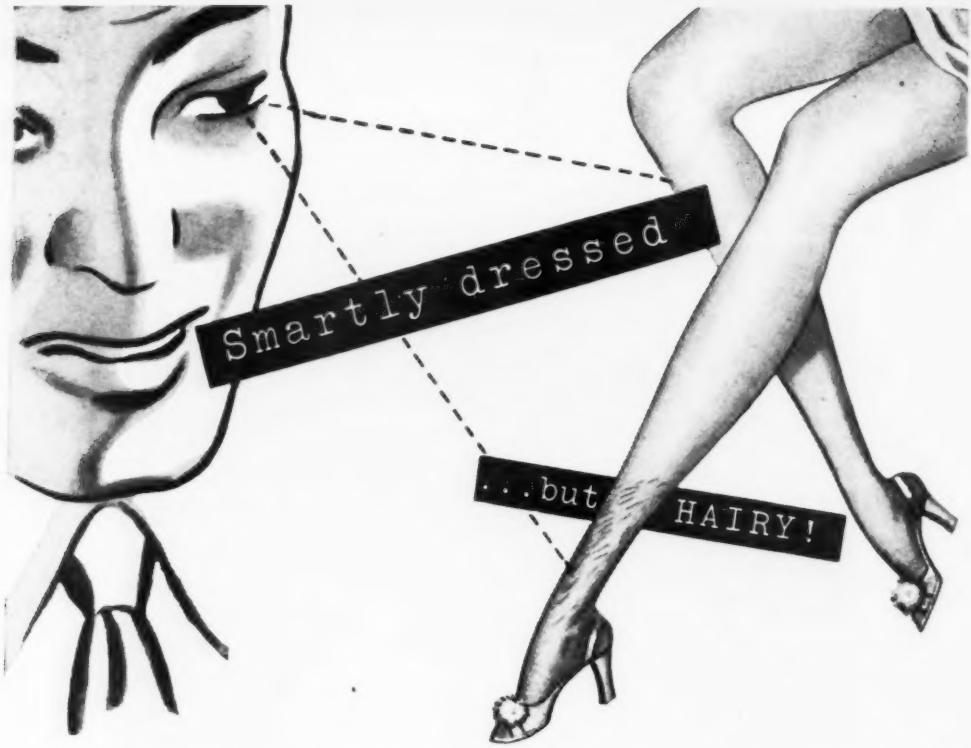

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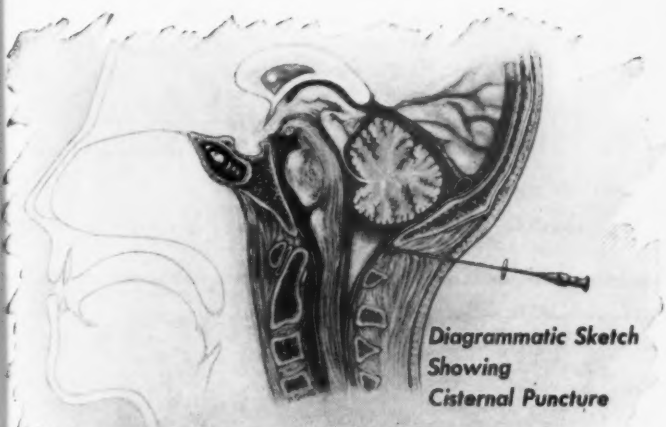

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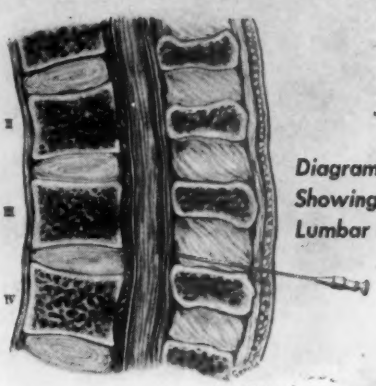

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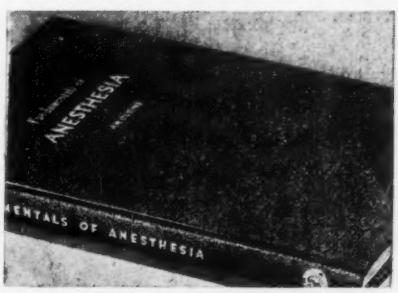

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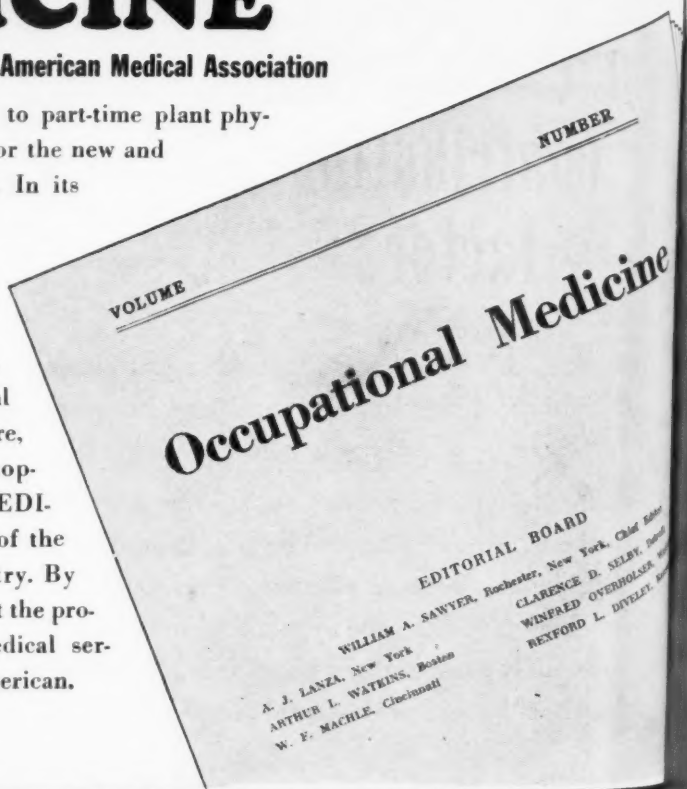

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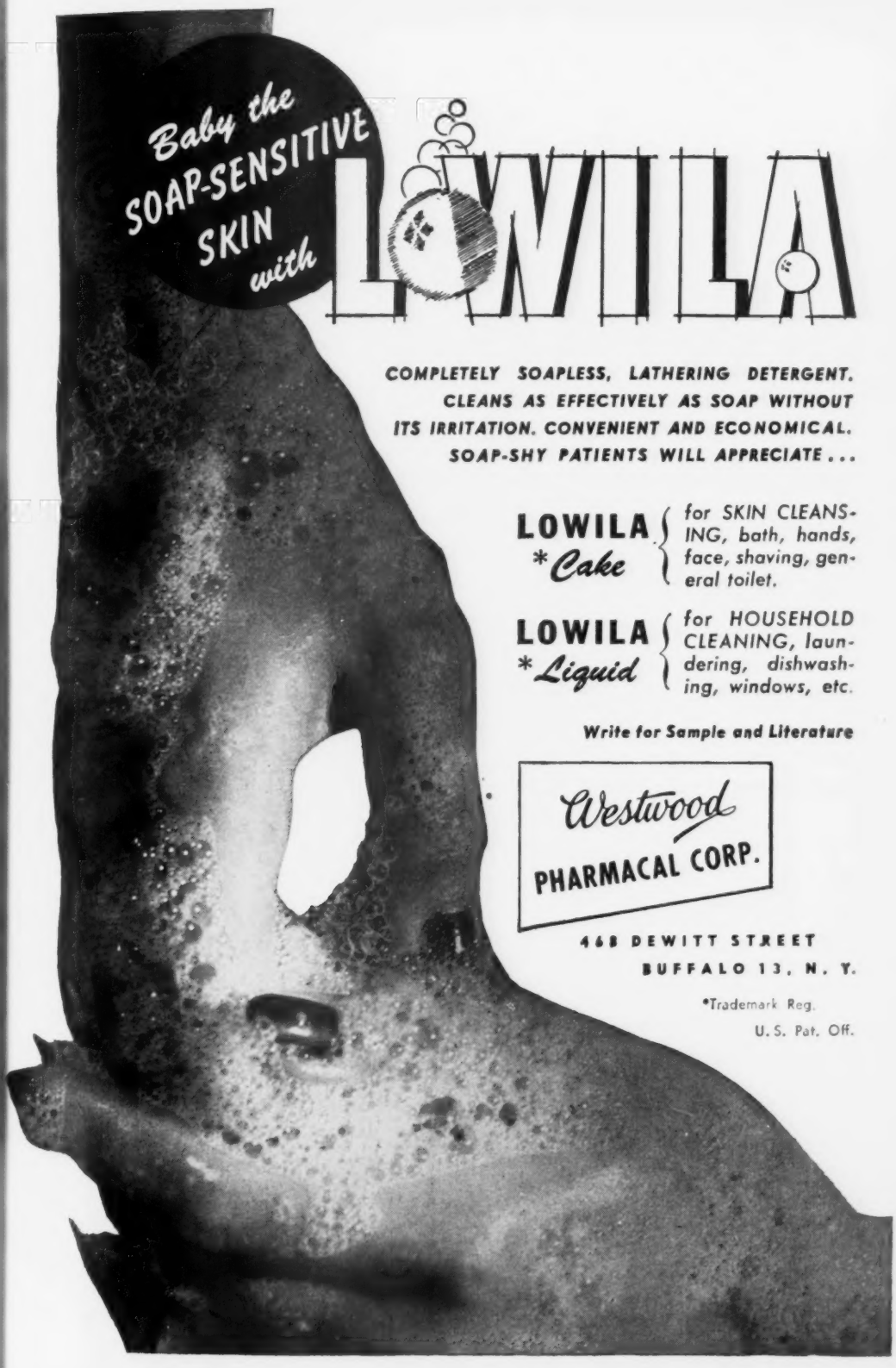

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